Biological therapy in Sjögren's syndrome : outcomes and evaluation

Meiners, Petra

Biological therapy in Sjögren's syndrome
Outcomes and evaluation

ISBN: 978-90-367-6971-6
ISBN: 978-90-367-6970-9 (ebook)
Bookdesign: Sgaar Groningen
Printed by: Drukkerij van der Eems Heerenveen

rijksuniversiteit
groningen

Biological therapy in Sjögren's syndrome

Outcomes and evaluation

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 14 mei 2014 om 12.45 uur

door

Petra Mariëlle Meiners

geboren op 4 augustus 1979
te Groningen

Promotores
Prof. dr. A. Vissink
Prof. dr. H. Bootsma
Prof. dr. F.K.L. Spijkervet
Prof. dr. F.G.M. Kroese

Beoordelingscommissie
Prof. dr. T.W.J. Huizinga
Prof. dr. F.R. Rozema
Prof. dr. J.M. van Laar

Paranimfen
drs. E.W.J. de Boer
dr. M. Jalving

Smooth seas never made a skilled sailor

Contents

Chapter 1

Introduction

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disease characterised primarily by chronic inflammation of the exocrine glands, in particular the salivary and lacrimal glands. This inflammatory process leads to changes in exocrine function and destruction of the glands. In turn, these changes result in a variety of complaints, the most common of which are a dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca). Other organs may also be affected by the inflammatory process, leading to extraglandular manifestations such as arthritis, vasculitis, nephritis and pulmonary involvement.[1] Almost all patients suffer from fatigue and may be restricted in their daily activities and participation in society, resulting in a reduced health-related quality of life (HR-QoL) and impaired socio-economic status.[2]

SS can be a primary idiopathic condition of unknown aetiology (primary SS; pSS), but the disease may also occur in the presence of another autoimmune disorder such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma and mixed connective tissue disease. In these cases, the condition is designated as secondary SS (sSS). SS has an estimated prevalence of about 0.3 to 1% in the general population and a female predominance (female to male ratio 9:1), making it the second most common systemic autoimmune disease after RA. It has, however, received far less research and therapeutic attention than, for example, SLE.[1,3]

There is a large diversity of initial clinical manifestations of SS, and these manifestations do not always present at the same time. Physicians and dentists sometimes treat a particular symptom of SS, unaware of an underlying systemic disease. As a result, misdiagnosis of patients with SS is common, as their symptoms are considered minor or vague, or mimick those of other diseases. Consequently, delayed diagnosis of SS is frequent. An extensive diagnostic delay can affect the patient's well-being, e.g., because of the anxiety that accompanies undiagnosed illnesses. It is presumed that early, accurate diagnosis of SS may enable adequate treatment of symptoms and prevent many of the systemic complications associated with the disease.[4] Overall, SS is a disabling disease and there is a clear need for development of adequate treatment modalities to reduce SS-related symptoms and to halt progression of the disease.

Classification and diagnosis

Many classification criteria for pSS have been suggested. The consensus criteria of the American-European Consensus Group (AECG, Vitalli et al 2002) are currently the most widely accepted and validated criteria (table 1).[5] The AECG classification criteria combine subjective symptoms of dry eyes and dry mouth with objective signs of keratoconjunctivitis sicca and xerostomia, and with serological and histopathological characteristics. Diagnosis of pSS requires 4 out of 6 criteria to be met, including a positive salivary gland biopsy or antibodies to SSA or SSB. The Sjögren's International Collaborative Clinical

Table 1. Revised American-European Consensus Group classification criteria for SS (2002).[5]

I. Ocular symptoms: a positive response to at least 1 of the following questions:
   1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   2. Do you have a recurrent sensation of sand or gravel in the eyes?
   3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least 1 of the following questions:
   1. Have you had a daily feeling of dry mouth for more than 3 months?
   2. Have you had recurrently or persistently swollen salivary glands as an adult?
   3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs-that is, objective evidence of ocular involvement defined as a positive result for a least 1 of the following 2 tests:
   1. Schirmer's I test, performed without anaesthesia (≤5 mm in 5 minutes)
   2. Rose Bengal score or other ocular dye score (e.g., Lissamin green; ≥4 according to Van Bijsterveld's scoring system)

IV. Histhopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least 1 of the following diagnostic tests:
   1. Unstimulated whole salivary flow rate (≤ 1.5 mL in 15 minutes)
   2. Parotid sialography showing delayed uptake, reduced concentration and/or delayed excretion of tracer
   3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:
   1. Antibodies to Ro/SSA or La/SSB antigens, or both

Revised rules for classification

For primary SS
In patients without any potentially associated disease, primary SS may be defined as follows:
a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, VI)
c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

For secondary SS
In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria:
Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficienty disease (AIDS)
Pre-existing lymphoma
Sarcoidosis
Graft versus host disease
Use of anticholinergic drugs (since a time shorter that 4-fold the half life of the drug)

Alliance Research Groups recently proposed an alternative set of criteria, the American College of Rheumatology (ACR, Shiboski et al 2012) classification criteria.[6] These ACR criteria differ from the AECG criteria by excluding criteria based upon symptoms of glandular manifestations and not distinguishing between pSS and sSS. Furthermore, having IgG4-related disease is an exclusion criterion in the ACR criteria, which is not the case yet for the AECG criteria. Labial salivary gland biopsies and serology remain the main criteria in both sets. Shiboski et al[6] found that, compared with the AECG criteria, the preliminary ACR criteria had higher sensitivity and similar specificity, while Rasmussen et al[7] compared the AECG and ACR criteria in 646 participants and found no clear evidence for increased value of the new ACR criteria over the AECG criteria from a clinical or biological perspective. Which set of criteria to use is an issue that remains to be clarified. Working groups from both the European League Against Rheumatism (EULAR) and the ACR are currently working on merging the AECG and ACR criteria into a single set.

Importantly, regardless of the classification criteria used, their purpose is to define homogeneous study groups for clinical studies; these criteria sets are not intended for diagnostic purposes. Nevertheless, they are widely used as diagnostic tools for pSS. One should realize, however, that pSS can be present in a patient who does not completely fulfill these criteria.

Pathogenesis

The pathogenesis of pSS is extremely complex. Different cell types, chemokines and cytokines are thought to be involved, but the complete mechanism of pSS remains to be elucidated. Histopathological features in pSS reflect the autoimmune process, of which the most pathognomonic histological finding in salivary gland biopsies is the presence of progressive lymphocytic infiltrates around striated ducts. These infiltrates consists mainly of T- and B-cells, whereas other cell types (including plasma cells, macrophages and dendritic cells) compromise a smaller percentage of infiltrated cells.[8] The epithelial cells of striated ducts have a dual function. These epithelial cells are not only a likely target of the autoimmune attack, but also exert important immunological functions by virtue of the production of cytokines and chemokines and their role as antigen presenting cells.[9-11]

Pronounced B-cell hyperactivity appears to be a hallmark of pSS, which is reflected by one or more of the following serological manifestations: increased serum IgG levels, presence of cryoglobulins, and the presence of autoantibodies such as rheumatoid factor (RF) and antinuclear antibodies (ANA), including antibodies against Ro/SSA and La/SSB antigens.[1]

Chemokines drive the pathogenetic process by recruiting lymphoid cells to sites of inflammation. Elevated levels of these chemokines are found in glandular tissue, saliva, tears and serum of pSS patients.[12-15] Initially, pro-inflammatory chemokines such as CXCL10 are required for the recruitment of activated/effector lymphocytes. At this

Table 2. American College of Rheumatology criteria for SS (2012).[6]

I. Positive serum anti-Ro/SSA and/or anti-La/SSB or (positive RF and ANA titer ≥1:320)
II. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus per 4 mm^2
III. Keratoconjuctivitis sicca with ocular staining score ≥3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years)

Rules for classification

The classification of SS, which applies to individuals with signs/symptoms that may be suggestive of SS, will be met in patients who have at least 2 of the following 3 objective features previously described.

Exclusion criteria

History of head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficienty disease (AIDS)
Sarcoidosis
Amyloidosis
Graft versus host disease
IgG4-related disease

early stage of the disease, the infitrates are not organized as ectopic lymphoid tissue, and most lymphoid cells are $CD4^+$ T-cells.[16] Ongoing inflammation may result in development of ectopic lymphoid tissue with segregated T- and B-cell areas, germinal center-like structures and high endothelial venules. Homeostatic chemokines, including CXCL13, CCL19 and CCL21, are involved in this process.[11,17-19]

This local microenvironment of the inflamed glandular tissue is well-equipped to promote B-cell survival, activation, plasma cell formation and to sustain autoantibody formation. Analysis of the immunoglobulin genes shows the presence of clonal expansion of B-cells and plasma cells at these sites, providing further evidence for the hyperactive state of B-cells.[19] The coordinated action of B-cell receptor ligation, T-cell mediated CD40 stimulation and TLR-engagement in conjunction with the appropriate cytokines is responsible for the activation of B-cells. Aberrant signaling of the B-cell receptor could play a role in the development of pSS.[11]

In pSS critical cytokines involved in B-cell survival and activation are over expressed in salivary gland tissue, saliva and serum. These cytokines comprise both the type I IFN induced cytokines BAFF (B-cell-activating factor) and APRIL (a proliferation-inducing ligand).[21] In pSS, levels of serum BAFF and APRIL correlate well with disease parameters, including focus score (amount of infiltrates) in minor salivary glands, serum IgG levels and autoantibody titers (anti-SSA, anti-SSB, RF).[22-24] These findings strongly argue that BAFF and APRIL are involved in B-cell hyperactivity and B-cell autoimmunity.

Plasma cell formation is an IL-21 dependent process. IL-21 is secreted by $CD4^+$ Tf-helper

cells, and is largely dependent on IL-6. Also the above mentioned cytokines are significantly overexpressed in patients with pSS, reflecting the activation of the humoral immune system. The T-cell dependent hyperactivation of B-cells results in (auto-) antibody formation, ultimately leading to the hypergammaglobulinemia and contributes to the autoimmune destruction of the target tissues. In addition, B-cells also exert antibody independent, and immune regulatory functions, by their production and secretion of a wide variety of cytokines, including IL-6, IL-10, interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNFα).[11]

Treatment

Until recently, therapy for SS was largely limited to symptomatic treatments that improve sicca features,[25] and most of the *traditional* disease-modifying antirheumatic drugs (DMARDs) used in RA and SLE have been tried in pSS with limited results.[26-32] However, the progress that has been made in understanding the pathogenic process of pSS provided new targets for therapeutic intervention. At present, biological agents that target specific cells or cytokines involved in immune responses have been introduced in the treatment of various systemic autoimmune diseases. These *biological* DMARDs enhance or replace conventional immunosuppressive therapy; however, none of these agents has yet been approved for the treatment of pSS. Biological DMARDs such as tumour necrosis factor α (TNF-α) inhibitors,[33-35] interferon α[35] and B-cell depletion therapy (anti-CD20 (rituximab),[37-40] anti-CD22 (epratuzumab)[40]) have been studied in pSS, with B-cell depleting therapy using rituximab showing the most promising results.

Rituximab is a chimeric anti-CD20 monoclonal antibody that binds to the B-cell surface antigen CD20. CD20 is expressed in the surface of pre-B, transitional B and mature B-lymphocytes, and is lost at the plasma cell stage. CD20 mediates B-cell activation, proliferation and differentiation.[42,43] CD20 may play an important role in the generation of T-cell dependant antibody response.[44] Given the central role of B-cells in the pathogenetic process, CD20 is a promising target for treatment of rheumatic autoimmune diseases including pSS.[45] In pilot trials, it has been shown that treatment with rituximab improves pSS related signs and symptoms.[46] Phase III trials investigating whether rituximab is indeed an asset in the treatment of pSS are currently underway.

Little is known about the clinical effects of targeting T-cell mediated responses with biological therapy in pSS patients. Abatacept is a fully human fusion molecule of cytotoxic T-lymphocyte antigen 4 (CTLA-4) and IgG-Fc that modulates CD28-mediated T-cell co-stimulation. Co-stimulation between antigen-presenting cells and T-cells, and between B-cells and T-cells is an essential step in T-cell-dependent immune responses including autoimmune responses.[47] Abatacept has demonstrated consistently good safety and efficacy profiles in RA[48-51] and polyarticular juvenile idiopathic arthritis.[52] While randomised controlled trials (RCTs) in SLE initially did not meet the pre-specified primary endpoints, post hoc analyses using alternative definitions for clinical response

suggested possible beneficial effects in active lupus arthritis and proliferative nephritis.[53] Given the mechanism of action of abatacept and the recognized role of T- and B-cells (cellular and humoral response) in pSS, selective modulation of co-stimulation represents a rational therapeutic option in pSS that is worth exploring.

Assessing disease activity

The use of measures to quantify the extent and severity of pSS in a standardised way is crucial to the development of effective therapies to treat pSS. The EULAR task force recently introduced the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), an index to be completed by the physician, to assess systemic complications of pSS[54] and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), a patient-administered questionnaire, to assess patient symptoms (dryness, pain and fatigue).[55] Seror and colleagues[56] investigated the ESSDAI for its sensitivity to measure change in disease activity over time in patient profiles. However, prospective data on the responsiveness of ESSDAI after therapeutic intervention are currently lacking. Furthermore, no data on the responsiveness of ESSPRI are available. Therefore, it needs to be assessed whether these indices are indeed sensitive measures of change in disease activity after therapeutic intervention. If established as sensitive measures of change in disease activity and symptoms in pSS patients, these indices may facilitate the evaluation of new treatment options in pSS. In addition to rating disease activity, ESSDAI and ESSPRI may also be useful for monitoring pSS progression and as a tool for assessing the efficacy of symptomatic or interventional treatment.

Outline of this thesis

This thesis covers several topics in SS and pSS. The first goal of this thesis is to objectify the impact of having SS on patients' functioning and daily activity, in order to clarify the need for the development of novel treatment options for SS, and provide a rationale for performing research in this field. The second focus of the research described in this thesis is the currently available symptomatic and interventional treatment for pSS. The efficacy and safety of 2 promising biological therapies (rituximab and abatacept) are evaluated. The effect of rituximab and abatacept was studied in pSS patients and not in sSS patients, as in sSS patients there is always another autoimmune disorder present which limits assessing whether the observed treatment effect will be due to the SS component, to the other autoimmune component or both. Finally, the extent and severity of pSS are assessed using the recently developed ESSDAI and ESSPRI. Thus, the potential of both tools to monitor the effect of interventional treatment in pSS is assessed.

The impact of SS on HR-QoL and socio-economic status of patients with SS is described in chapter 2. This impact was explored in a cross-sectional study in which HR-QoL, employment and disability in pSS and sSS patients were compared with the general Dutch

population. The purpose of this study was to assess the necessity for treatment in SS patients and provide a rationale for performing research in this field.
Although there is currently no curative or causal treatment for SS, various supportive and palliative treatment options are available, and targeted approaches (biological DMARDs) are in development. Chapter 3 summarizes the current management of the glandular and extraglandular manifestations of SS and discusses prospects, focusing on better understanding of disease progression and more effective treatment.

In chapter 4, treatment of pSS with B-cell depleting therapy with rituximab is discussed. In chapter 4.1, a double-blind RCT with rituximab is described. In this prospective study, 20 pSS patients were treated with rituximab and 10 pSS patients with placebo. Emphasis was placed on the effect of rituximab on clinical symptoms and signs of pSS. Based on the promising results of this RCT, an extension study was performed to study the efficacy of retreatment with rituximab, which is described in chapter 4.2. The outcomes of various trials with rituximab in pSS patients are critically discussed in chapter 4.3.

In chapter 5, 2 recently developed disease activity indices, namely ESSDAI and ESSPRI, are tested for their sensitivity in measuring change after therapeutic intervention. We investigated whether the responsiveness of ESSDAI and ESSPRI is sufficient to assess a clinically relevant treatment effect of rituximab. In chapter 5.1, responsiveness of ESSDAI and ESSPRI is prospectively analysed in 28 pSS patients treated with rituximab. To further examine the utility of ESSDAI for clinical studies, we assessed the responsiveness of ESSDAI in our double-blind RCT with rituximab, which is described in chapter 5.2.

Chapter 6 presents the results of the Active Sjögren Abatacept Pilot (ASAP) study. In this open-label proof of concept study, the efficacy and safety of abatacept treatment in patients with pSS are evaluated. Emphasis was placed on the effect of abatacept on clinical symptoms and signs of pSS. Disease activity was assessed with ESSDAI and ESSPRI.

The results of the various studies are summarised and discussed in chapter 7. The general discussion focuses on the interpretation, implications and potential applications of the results of various trials with biological DMARDs, and future perspectives and possibilities for further research in this area are explored. Chapter 8 is the summary in Dutch.

References

1 Fox RI. Sjögren's syndrome. Lancet 2005;366:321-31.

2 Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology 2009;48:1077-82.

3 Hansen A, Lipsky PE, Dorner T. Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. Curr Opin Rheumatol 2005;17:558-65.

4 Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med 2004;164:1275-84.

5 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. Ann Rheum Dis 2002;61:554-8.

6 Shiboski SC, Shiboski CH, Criswell L, et al. American college of rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's international collaborative clinical alliance cohort. Arthritis Care Res 2012;64:475-87.

7 Rasmussen A, Ice JA, Li H, et al. Comparison of the American-European consensus group Sjögren's syndrome classification criteria to newly proposed American college of rheumatology criteria in a large, carefully characterised SICCA cohort. Ann Rheum Dis 2014;73:31-8.

8 Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjögren's syndrome. J Autoimmun 2010;34:400-7.

9 Manoussakis MN, Kapsogeorgou EK. The role of intrinsic epithelial activation in the pathogenesis of Sjögren's syndrome. J Autoimmun 2010;35:219-24.

10 Routsias JG, Tzioufas AG. B-cell epitopes of the intracellular autoantigens Ro/SSA and La/SSB: tools to study the regulation of the autoimmune response. J Autoimmun 2010;35:256-64.

11 Kroese FGM, Abdulahad WH, Haacke E, et al. B-cell hyperactivity in primary Sjögren's syndrome. Exp Rev Clin Immunol 2014 [In press].

12 Boumba D, Skopouli FN, Moutsopoulos HM. Cytokine mRNA expression in the labial salivary gland tissues from patients with primary Sjögren's syndrome. Br J Rheumatol 1995;34:326-33.

13 Fox RI, Kang HI, Ando D, et al. Cytokine mRNA expression in salivary gland biopsies of Sjögren's syndrome. J Immunol 1994;152:5532-9.

14 Rollins BJ. Chemokines. Blood 1997;90:909-28.

15 Szyszko EA, Brokstad KA, Oijordsbakken G, et al. Salivary glands of primary Sjögren's syndrome patients express factors vital for plasma cell survival. Arthritis Res Ther 2011;13:R2.

16 Mitsias DI, Tzioufas AG, Veiopoulou C, et al. The Th1/Th2 cytokine balance changes with the progress of the immunopathological lesion of Sjögren's syndrome. Clin Exp Immunol 2002;128:562-8.

17 Amft N, Curnow SJ, Scheel-Toellner D, et al. Ectopic expression of the B-cell-attracting chemokine BCA-1 (CXCL13) on endothelial cells and within lymphoid follicles contributes to the establishment of germinal center-like structures in Sjögren's syndrome. Arthritis Rheum 2001;44:2633-41.

18 Barone F, Bombardieri M, Manzo A, et al. Association of CXCL13 and CCL21 expression with the progressive organisation of lymphoid-like structures in Sjögren's syndrome. Arthritis Rheum 2005;52:1773-84.

19 Jonsson MV, Skarstein K, Jonsson R, et al. Serological implications of germinal center-like structures in primary Sjögren's syndrome. J Rheumatol 2007;34:2044-9.

20 Hamza N, Bootsma H, Yuvaraj S, et al. Persistence of immunoglobulin-producing cells in parotid salivary glands of patients with primary Sjögren's syndrome after B-cell depletion therapy. Ann Rheum Dis 2012;71:1881-7.

21 Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol 2009;9:491-502.

22 Jonsson R, Theander E, Sjostrom B, et al. Autoantibodies present before symptom onset in primary Sjögren syndrome. JAMA 2013;310:1854-5.

23 Mariette X, Roux S, Zhang J, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjögren's syndrome. Ann Rheum Dis 2003;62:168-71.

24 Pers JO, d'Arbonneau F, Devauchelle-Pensec V, et al. Is periodontal disease mediated by salivary BAFF in Sjögren's syndrome? Arthritis Rheum 2005;52:2411-4.

25 Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjögren syndrome: a systematic review. JAMA 2010;304:452-60.

26 Fox PC, Datiles M, Atkinson JC, et al. Prednisone and piroxicam for treatment of primary Sjögren's syndrome. Clin Exp Rheumatol 1993;11:149-56.

27 Dawson LJ, Caulfield VL, Stanbury JB, et al. Hydroxychloroquine therapy in patients with primary Sjögren's syndrome may improve salivary gland hypofunction by inhibition of glandular cholinesterase. Rheumatology 2005;44:449-55.

28 Kruize AA, Hene RJ, Kallenberg CG, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. Ann Rheum Dis 1993;52:360-4.

29 Skopouli FN, Jagiello P, Tsifetaki N, et al. Methotrexate in primary Sjögren's syndrome. Clin Exp Rheumatol 1996;14:555-8.

30 Price EJ, Rigby SP, Clancy U, et al. A double blind placebo controlled trial of azathioprine in the treatment of primary Sjögren's syndrome. J Rheumatol 1998;25:896-9.

31 Thanou-Stavraki A, James JA. Primary Sjögren's syndrome: current and prospective therapies. Semin Arthritis Rheum 2008;37:273-92.

32 van Woerkom JM, Kruize AA, Geenen R, et al. Safety and efficacy of leflunomide in primary Sjögren's syndrome: a phase II pilot study. Ann Rheum Dis 2007;66:1026-32.

33 Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomised, controlled trial of remicade in primary Sjögren's syndrome (TRIPSS). Arthritis Rheum 2004;50:1270-6.

34 Zandbelt MM, de Wilde P, van Damme P, et al. Etanercept in the treatment of patients with primary Sjögren's syndrome: a pilot study. J Rheumatol 2004;31:96-101.

35 Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjögren's syndrome: a twelve-week randomised, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240-5.

36 Cummins MJ, Papas A, Kammer GM, et al. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. Arthritis Rheum 2003;49:585-93.

37 Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541-4.

38 Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007;57:310-7.

39 Meijer JM, Pijpe J, Bootsma H, et al. The future of biologic agents in the treatment of Sjögren's syndrome. Clin Rev Allergy Immunol 2007;32:292-7.

40 Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005;52:2740-50.

41 Steinfeld SD, Tant L, Burmester GR, et al. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phase I/II study. Arthritis Res Ther 2006;8:R129.

42 Tedder TF, Boyd AW, Freedman AS, et al. The B-cell surface molecule B1 is functionally linked with B-cell activation and differentiation. J Immunol 1985;135:973-9.

43 Tedder TF, Forsgren A, Boyd AW, et al. Antibodies reactive with the B1 molecule inhibiT-cell cycle progression but not activation of human B lymphocytes. Eur J Immunol 1986;16:881-7.

44 Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T-cell-independent antibody responses. J Clin Invest 2010;120:214-22.

45 Engel P, Gomez-Puerta JA, Ramos-Casals M, et al. Therapeutic targeting of B-cells for rheumatic autoimmune diseases. Pharmacol Rev 2011;63:127-56.

46 Kallenberg CG, Vissink A, Kroese FG, et al. What have we learned from clinical trials in primary Sjögren's syndrome about pathogenesis? Arthritis Res Ther 2011;13:205.

47 Moreland L, Bate G, Kirkpatrick P. Abatacept. Nat Rev Drug Discov 2006;5:185-6.

48 Kremer JM, Russell AS, Emery P, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis 2011;70:1826-30.

49 Bathon J, Robles M, Ximenes AC, et al. Sustained disease remission and inhibition of radiographic progression in methotrexate-naive patients with rheumatoid arthritis and poor prognostic factors treated with abatacept: 2-year outcomes. Ann Rheum Dis 2011;70:1949-56.

50 Schiff M, Keiserman M, Codding C, et al. Clinical response and tolerability to abatacept in patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the ATTEST study. Ann Rheum Dis 2011;70:2003-7.

51 Genovese MC, Schiff M, Luggen M, et al. Long-term safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy. J Rheumatol 2012;39:1546-54.

52 Ruperto N, Lovell DJ, Quartier P, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum 2010;62:1792-802.

53 Mok CC. Abatacept for systemic lupus erythematosus: the outlook. Expert Opin Biol Ther 2012;12:1559-61.

54 Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

55 Seror R, Ravaud P, Mariette X, et al. EULAR Sjögren's syndrome patient reported index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. Ann Rheum Dis 2011;70:968-72.

56 Seror R, Mariette X, Bowman S, et al. Accurate detection of changes in disease activity in primary Sjögren's syndrome by the European league against rheumatism Sjögren's syndrome disease activity index. Arthritis Care Res 2010;62:551-8.

Chapter 2

Health-related quality of life, employment and disability in patients with Sjögren's syndrome

Petra M Meiners*[1], Jiska M Meijer*[1], James JR Huddleston Slater[1,2], Fred KL Spijkervet[1], Cees G M Kallenberg[3], Arjan Vissink[1], Hendrika Bootsma[3]

* These authors contributed equally to this paper

Departments of [1]Oral and Maxillofacial Surgery, [2]Oral Health Care and Clinical Epidemiology, and [3]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, The Netherlands

Rheumatology 2009;48(9):1077-82

ABSTRACT

Objective. To compare health-related quality of life (HR-QoL), employment and disability of primary (pSS) and secondary (sSS) Sjögren's syndrome (SS) patients with the general Dutch population.

Methods. HR-QoL, employment and disability were assessed in SS patients regularly attending the University Medical Center Groningen (n=235). HR-QoL, employment and disability were evaluated with the Short Form-36 questionnaire (SF-36) and an employment and disability questionnaire. Results were compared with Dutch population data (matched for gender and age). Demographical and clinical data associated with HR-QoL, employment and disability were assessed.

Results. Response rate was 83%. SS patients scored lower on HR-QoL than the general Dutch population. sSS patients scored lower on physical functioning, bodily pain and general health than pSS patients. Predictors for reduced HR-QoL were fatigue, tendomyalgia, articular involvement, use of artificial saliva, use of antidepressants, comorbidity, male gender and eligibility for disability compensation (DC). Employment was lower and DC rates were higher in SS patients compared with the Dutch population.

Conclusion. SS has a large impact on HR-QoL, employment and disability.

INTRODUCTION

Sjögren's syndrome (SS) is a chronic, systemic, lymphoproliferative autoimmune disease affecting the exocrine glands.[1] The salivary and lacrimal glands are most commonly affected, resulting in dry mouth and dry eyes. Extraglandular involvement can occur in SS, and includes pulmonary disease, renal disease and vasculitis. Moreover, almost all patients suffer from fatigue. SS can be primary (pSS) or secondary (sSS), the latter being associated with other autoimmune diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). The estimated prevalence of SS in the general population is between 0.5 and 2%, which makes SS, after RA, the most common systemic autoimmune disease.[2,3]

Rheumatological conditions have a major impact on patients. Apart from the symptoms mentioned above, patients may be restricted in their activities and their participation in society, resulting in a reduced health-related quality of life (HR-QoL) and an impaired socio-economic status. The latter may result in lower employment rates and more disability as compared with the general population.[4]

SS is known to affect patients' physical, psychological and social functioning,[5] but the impact of SS on HR-QoL, and especially on employment and disability, has not been studied extensively. Studies available are either performed in a small series of SS patients[6,7] or aimed mainly at comparison with other rheumatic diseases,[6-9] fatigue[9] and psychological status,[8] or at developing new tools for measuring fatigue and general discomfort in pSS patients.[10] Comparison between pSS and sSS has occasionally been described for HR-QoL,[7,9] but not for employment and disability. The aim of this study was, therefore, to evaluate HR-QoL, employment and disability in a large cohort of Dutch SS patients, to relate outcomes to clinical and demographic data in this patient cohort, and to compare these data with those available for the general Dutch population. In addition, HR-QoL, employment and disability were compared between pSS and sSS patients, since it was hypothesized that the disease burden of sSS might differ from that of pSS due to coexisting autoimmune disease(s).

PATIENTS AND METHODS

Patients

SS patients (185 pSS and 50 sSS) regularly attending the departments of rheumatology and clinical immunology and oral and maxillofacial surgery of the University Medical Center Groningen (UMCG), The Netherlands, were enrolled in this study. All patients were >18 years old and fulfilled the revised American-European Consensus Group (AECG) criteria.[11] All patients participating in this study were followed according to protocol, and, therefore, data on extraglandular manifestations (EGMs) were available for all patients. Ethical approval for this study was obtained from the local Institutional Review

Board (Medisch Ethische Toetsingscommissie of the University Medical Center Groningen, The Netherlands).

Methods

Demographical and clinical data were obtained by chart review. EGMs were defined in accordance with previous studies.[12,13] Tendomyalgia, skin involvement other than cutaneous vasculitis, oesophageal involvement, bladder involvement and thrombocytopenia are commonly observed symptoms and signs, and, thus, were also considered as EGMs. Moreover, at every visit the rheumatologists systematically evaluated the presence of EGMs.

Questionnaires were sent by regular mail to all patients. Six weeks after sending the questionnaires, patients who had not responded were approached by phone once, to ask for participation.

In the first questionnaire, patients were asked whether they suffered from arthralgia and/or tendomyalgia, fatigue, dry mouth and dry eyes. In addition, it was asked which symptom they considered to be their most severe complaint.

To evaluate HR-QoL, a validated Dutch translation of the Short Form-36 (SF-36) was used.[14] The SF-36 is a questionnaire consisting of 36 items, with 8 scales assessing 2 dimensions, viz. physical and mental health functioning. Scales and summary scores vary from 0 to 100, with 0 being the worst possible health status and 100 representing the best possible health status.

The third questionnaire focussed on level of education, employment and disability. In The Netherlands, an individual who is judged to be impaired by ≥80% is entitled to full disability compensation (DC). Individuals impaired by 15 to 80% are entitled to partial DC.

Age- and gender-matched data for the general Dutch population on the SF-36 were obtained from Aaronson et al.[14] Data regarding employment and DC were obtained from the Dutch Office of Statistics (Centraal Bureau voor Statistiek, CBS, Voorburg, The Netherlands).

Statistical analysis

T-tests and X^2 tests were used for the comparison of demographic data, HR-QoL, employment and receiving DC between responders and non-responders, between pSS and sSS patients, and between SS patients and the general Dutch population. Alpha was set at 5%. Correlation between disease duration and HR-QoL was evaluated with a Pearson's correlation test.

To create effect models, univariate analyses were performed for each predictor variable on the outcomes (HR-QoL, employment and receiving DC). If variables were found to be significant, p values were used in the further development of the model. Predictors with a p value ≤0.2 were simultaneously entered into a multivariable model, after which

Table 1. Patients' characteristics.

Characteristics	All responding SS patients n=195	pSS n=154	sSS n=41	p Value (pSS vs. sSS)
Age, mean±SD, years	55.5±15.0	54.6±15.1	58.9±14.2	0.103
Age at diagnosis, mean±SD, years	45.7±15.7	45.5±15.3	46.5±17.1	0.715
Female gender, n (%)	179 (91.8)	143 (92.9)	36 (87.8)	0.197
Partner, n (%)	153 (78.5)	121 (78.6)	32 (78.0)	0.769
Disease duration, mean±SD, years	9.7±8.8	9.0±8.0	12.5±11.0	0.121
Immunological features				
Focus score, mean±SD	2.7±1.8	2.7±2.0	2.5±2.0	0.716
ANA positive, n (%)	189 (96.9)	151 (98.1)	38 (92.7)	0.109
Anti-Ro/SSA positive, n (%)	155 (79.5)	129 (83.8)	26 (63.4)	0.014
Anti-La/SSB positive, n (%)	107 (54.9)	90 (58.4)	17 (41.5)	0.077
IgG, mean±SD, g/L	18.6±7.2	18.8±6.8	17.7±8.3	0.405
IgA, mean±SD, g/L	2.8±1.3	2.7±1.2	3.2±1.5	0.023
IgM, mean±SD, g/L	1.4±1.0	1.4±1.1	1.3±0.8	0.629
RF, mean±SD, kIU/L	106.2±190.2	99.5±195.6	131.2±168.7	0.343
Extraglandular manifestations (n, %)	185 (94.9)	144 (93.5)	41 (100)	0.112
Articular involvement[a]	110 (56.4)	80 (51.9)	30 (73.2)	0.017
Raynaud's phenomenon	84 (43.1)	67 (43.5)	17 (41.5)	0.789
Tendomyalgia	80 (41.0)	64 (41.6)	16 (39.0)	0.746
Pulmonary involvement	33 (16.9)	25 (16.2)	8 (19.5)	0.631
Lymphoproliferative disease	30 (15.4)	24 (15.6)	6 (14.6)	0.869
Cutaneous vasculitis	28 (14.4)	22 (14.3)	6 (14.6)	0.967
Peripheral neuropathy	26 (13.3)	20 (13.0)	6 (14.6)	0.794
Skin involvement other than cutaneous vasculitis[a]	22 (11.3)	13 (8.4)	9 (22.0)	0.047
Bladder involvement	22 (11.3)	18 (11.7)	4 (9.8)	0.719
Lymphadenopathy	21 (10.8)	19 (12.3)	2 (4.9)	0.168
Renal involvement	19 (9.7)	14 (9.1)	5 (12.2)	0.560
Autoimmune thyroiditis	19 (9.7)	16 (10.4)	3 (7.3)	0.548
Autoimmune hepatitis	12 (6.2)	11 (7.1)	1 (2.4)	0.262
Esophageal involvement	9 (4.6)	7 (4.5)	2 (4.9)	0.872
Fever	8 (4.1)	7 (4.5)	1 (2.4)	0.541
Serositis	6 (3.1)	5 (3.2)	1 (2.4)	0.785
Myositis	5 (2.6)	3 (1.9)	2 (4.9)	0.295
CNS involvement	5 (2.6)	5 (3.2)	-	0.241
Thrombocytopenia	2 (1.0)	2 (1.3)	-	0.337
Acute pancreatitis	1 (0.5)	1 (0.6)	-	-
Second autoimmune disease				
None	154 (79.0)	154 (100)		
SLE	19 (9.7)		19 (46.3)	
RA	16 (8.2)		16 (39.0)	
Other	6 (3.1)		6 (14.6)	
Comorbidity, n (%)[b]	75 (38.5)	59 (38.3)	16 (39.0)	0.957
Therapy, n (%)				
Artificial tears	151 (77.4)	119 (77.3)	32 (78.0)	0.711
Oral moisturising gel	46 (23.6)	37 (34.0)	9 (22.0)	0.840
Artificial saliva	20 (10.3)	16 (10.4)	4 (9.8)	0.942
Pilocarpine	18 (9.2)	15 (9.7)	3 (7.3)	0.663
NSAIDs	47 (24.1)	31 (20.1)	16 (39.0)	0.012
Antimalarial drugs	31 (15.9)	20 (13.0)	11 (26.8)	0.031
Oral corticosteroids	26 (13.3)	20 (13.0)	6 (14.6)	0.783
Rituximab	20 (10.3)	19 (12.3)	1 (2.4)	0.036
Other immunosuppresives	17 (8.7)	9 (5.8)	8 (19.5)	0.006
Antidepressants	18 (9.2)	14 (9.1)	4 (9.8)	0.769

[a]Extraglandular manifestation that affect sSS patients significantly more frequently than pSS patients.[b]Comorbidity unrelated to SS. SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; CNS, central nervous system.

Table 2. SF-36 scores for SS patients and the general Dutch population.

SF-36 scales and summary scores	GDP n=195	RSS n=195	p Value (RSS vs. GDP)	pSS n=154	sSS n=41	p Value (pSS vs. sSS)
Physical functioning	74.8 (25.8)	59.2 (26.0)	0.000	62.0 (25.1)	48.9 (27.0)	0.004
Physical role functioning	70.3 (36.3)	41.0 (42.9)	0.000	44.0 (42.7)	29.1 (41.9)	0.058
Bodily pain	68.7 (25.6)	64.7 (24.4)	0.136	68.0 (23.0)	52.1 (25.7)	0.000
General health	65.7 (21.5)	40.3 (18.2)	0.000	41.9 (18.4)	34.2 (16.3)	0.018
Vitality	63.8 (21.0)	45.2 (20.1)	0.000	46.0 (20.4)	42.0 (18.9)	0.266
Social functioning	81.3 (25.6)	63.1 (26.2)	0.000	64.5 (26.6)	57.9 (24.5)	0.152
Emotional role functioning	79.7 (34.4)	70.0 (41.4)	0.005	71.5 (41.5)	63.9 (40.9)	0.324
Mental health	73.3 (19.0)	70.3 (18.4)	0.055	70.6 (18.9)	69.0 (16.8)	0.627
PCS	73.0 (24.6)	51.7 (23.7)	0.000	53.3 (23.6)	44.7 (23.2)	0.055
MCS	74.5 (21.1)	63.3 (21.2)	0.000	64.0 (21.2)	60.5 (21.4)	0.385

Values are given as mean±SD. GDP, general Dutch population; RSS, all responding SS patients; PCS, physical component summary score; MCS, mental component summary score; n, number of patients.

backward elimination of predictors was used to remove non-significant predictors (p value to remove >0.10). Subsequently, predictors not included in the multivariable model were entered to determine whether they could now enter the model, after which the procedure of backward elimination of predictors was repeated. Variables in the final models were tested for possible interactions. All analyses were carried out using SPSS for Windows version 16.0.

RESULTS

Patient characteristics

A total of 196 patients (180 females, 16 males; mean age at diagnosis: 45.7±15.7 years) responded to the mail survey (83%). One patient returned the questionnaire incompletely and was therefore excluded. The mean±SD for age at the time of completing the questionnaire was 55.5±15.0 years; the mean±SD for disease duration was 9.7±8.8 years. One hundred and fifty-four patients (79%) were classified as pSS and 41 patients (21%) as sSS (table 1). Demographical data did neither differ between pSS and sSS patients nor between responders and non-responders.

The most frequently associated autoimmune disorders in sSS patients were SLE (46%) and RA (39%). Seventy-five patients (39%) suffered from at least 1 comorbid condition.

Artificial tears were used by 77% and antidepressants by 9% of patients. Non-steroidal anti-inflammatory drugs, antimalarial drugs and other immunosuppressants were used more frequently by sSS patients, whereas rituximab was more frequently prescribed in pSS patients.

EGMs were present in 185 patients (95%). The main EGMs were articular involvement, Raynaud's phenomenon and tendomyalgia. sSS patients suffered from articular and skin involvement more often than pSS patients. When restricting the EGMs to the EGMs defined in accordance with previous studies,[12,13] EGMs occured in 177 patients (91%; pSS 137; sSS 40).

Current symptoms

Almost all patients suffered from dry mouth (n=183; 94%), dry eyes (n=183; 94%), and fatigue (n=166; 85%). Fatigue was the most severe symptom in 78 patients (40%). Arthralgia and/or tendomyalgia was present in 148 patients (76%). The prevalence of sicca symptoms, fatigue and arthralgia and/or tendomyalgia was comparable between pSS and sSS patients.

HR-QoL

When compared with the general Dutch population, HR-QoL was significantly decreased in SS patients as demonstrated by reduced SF-36 scores on 6 out of the 8 scales and for the summary scores for physical and mental functioning (table 2).

sSS patients experienced a significantly lower HR-QoL than pSS patients on 3 of the 4 physical scales (physical functioning, bodily pain and general health); however, no differences were observed on the psychological scales. HR-QoL was comparable between sSS patients with either RA or SLE as the associated autoimmune disorder. Disease duration was not significantly correlated with any of the SF-36 scales. Highly educated patients scored significantly better on physical functioning (p=0.042) and mental health (p=0.005) compared with non-highly educated patients.

Multivariate regression analysis showed that fatigue, tendomyalgia, comorbidity, male gender and receiving DC were associated with a reduced physical component summary score (PCS) (table 3). Confounders were disease duration, use of NSAIDs and antidepressants and employment. No significant effect modifiers (interaction terms) were found.

Multivariate regression analysis for the mental component summary score (MCS) demonstrated that fatigue, articular involvement, use of artificial saliva, use of antidepressants and comorbidity were associated with a reduced MCS, whereas dry mouth was associated with a higher MCS (table 3). Receiving DC was a confounding factor for the determinants in the primary model for the MCS. No effect modifiers were found.

Socio-economic status

A total of 135 patients (69%) were of working age (18-65 years) (table 4). SS patients were significantly less often employed (p<0.001), worked fewer hours (p=0.015) and were less frequently full-time employed (p<0.01), compared with the Dutch population. In detail, approximately half of the SS patients (n=69) had paid employment. Only 7 patients (10%) worked full-time (≥36 hours). On average, SS patients worked 21.7±11.6 hours/week. The mean sick leave was 15.6±39.0 days during the past year (range 0-192 days). Highly educated patients were significantly more often employed than non-highly educated patients (p=0.001). No differences were found between pSS and sSS patients regarding employment variables.

Sixty-three working age patients (47%) received DC, because they were considered to be (partially) unfit for work (table 4). Twenty-eight of these patients (44%) were entitled to full DC. Moreover, 41 of the 63 patients receiving DC (65%) mentioned pSS, sSS or the associated rheumatic disease as the cause of receiving DC. No differences in DC were found between pSS and sSS patients or between highly educated and non-highly educated patients. A significantly higher percentage of SS patients received DC (47%) when compared with the general Dutch population (2%).

Multivariate regression analysis for employment (table 5) showed that a high level of education was associated with employment. Bladder involvement, use of oral moisturising gel, NSAIDs and oral corticosteroids, comorbidity and age at diagnosis were all negatively associated with employment. Autoimmune thyroiditis, use of artificial tears and age were confounding factors for these determinants. No interaction terms were found. Multivariate regression analysis for receiving DC (table 5) demonstrated that the

Table 3. Linear multivariate regression analyses for the PCS and MCS of the SF-36.

Variable	Model 1		Adjusted for confounding	
	ß (95% CI)	p Value	ß (95% CI)	p Value
PCS				
Fatigue	-24.26 (-33.07, -15.44)	0.000	-21.38 (-30.31, -12.46)	0.000
Tendomyalgia	-9.18 (-15.22, -3.13)	0.003	-7.62 (-14.22, -1.03)	0.024
Comorbidity	-18.51 (-24.97, -12.06)	0.000	-17.97 (-25.11, -10.82)	0.000
Male gender	-12.69 (-23.47, -1.92)	0.021	-11.38 (-22.11, -0.65)	0.038
Receiving DC	-9.64 (-15.95, -3.34)	0.003	-10.71 (-17.13, -4.29)	0.001
Disease duration, years			0.15 (-0.27, 0.56)	0.487
NSAID use			-4.37 (-11.67, 2.94)	0.239
Antidepressant use			-6.76 (-18.19, 4.67)	0.244
Employment			-0.95 (-2.31, 1.14)	0.217
MCS				
Fatigue	-15.97 (-24.48, -7.45)	0.000	-16.92 (-26.26, -7.57)	0.000
Dry mouth	17.93 (5.94, 29.91)	0.004	16.75 (2.50, 31.00)	0.022
Articular involvement	-7.63 (-13.65, -1.60)	0.008	-5.48 (-12.18, 1.22)	0.108
Artificial saliva use	-9.33 (-18.46, -0.21)	0.045	-12.58 (-22.97, -2.20)	0.018
Antidepressant use	-9.57 (-20.47, 1.32)	0.085	-11.32 (-24.18, 1.54)	0.084
Comorbidity	-9.49 (-15.74, -3.23)	0.003	-11.91 (-18.92, -4.89)	0.001
Receiving DC			-2.11 (-8.68, 4.45)	0.526

PCS, physical component summary score; MCS, mental component summary score; ß, regressioncoeficient; CI, confidence interval; DC, disability compensation; NSAIDs, non-steroidal anti-inflammatory drugs.

number of EGMs, use of artificial saliva and antimalarial drugs, comorbidity, high level of education, and male gender were associated with receiving DC. Age at diagnosis was negatively associated with receiving DC. Fatigue, skin involvement other than cutaneous vasculitis and use of pilocarpine were confounding factors for the determinants in the primary model for receiving DC. No interaction terms were found.

DISCUSSION

This study shows that SS has a large impact on HR-QoL, employment and disability as reflected by lower SF-36 scores and employment rates, and higher disability rates when compared with the general Dutch population. Moreover, analysis of HR-QoL revealed that sSS patients were more limited in physical activities than pSS patients. Although the results are obtained in a Dutch cohort of patients with SS, the striking differences in HR-QoL, employment and disability suggest that the results of our study are not limited to

Table 4. Education level, employment characteristics and DC in SS patients of working age.

Employment characteristics	GDP n=135	SS patients n=135	p Value (SS vs. GDP)	pSS patients n=109	sSS patients n=26	p Value (pSS vs. sSS)
Level of education, n (%)			<0.001			0.800
Low	31 (23.5)	5 (3.7)		5 (3.8)	0	
Middle	57 (43.2)	94 (69.6)		75 (57.7)	19 (57.6)	
High	44 (33.3)	33 (24.4)		26 (20.0)	7 (21.2)	
Unknown		3 (2.2)		3 (2.3)	0	
Paid employment, n (%)	109 (82.6)	69 (51.1)	<0.001	58 (53.2)	11 (42.3)	0.297
Full-time paid job, n (%)	26 (23.9)	7 (10.1)	<0.01	7 (12.1)	0	0.237
Hours worked per week, mean±SD	26.9±14.2	21.7±11.6	0.011	21.7±12.1	21.3±8.5	0.914
Sick leave per year, mean±SD, days	NA	15.6±39.0	NA	14.7±37.8	22.3±50.0	0.675
Receiving DC, n (%)	2 (1.5)	63 (46.7)	<0.001	49 (45.0)	14 (53.8)	0.267
Full DC, n (%)	NA	28 (44.4)	NA	21(42.9)	7 (50.0)	0.434
Disability percentage, mean±SD	NA	66.2±30.2	NA	63.6±30.0	75.8±30.0	0.246
Cause receiving DC						
pSS, sSS or associated rheumatic disease	NA	41 (65.1)	NA	33 (67.3)	8 (57.1)	
Other		7 (11.1)		6 (12.2)	1 (7.1)	
Unknown		15 (23.8)		10 (20.4)	5 (35.7)	

DC, disability compensation; GDP, general Dutch population; n, number of patients; NA, not available.

the Dutch population, but probably are generally applicable to SS patients when compared with healthy subjects.

Reduced HR-QoL in SS patients compared with normative data has been reported before, but these studies were performed in smaller populations.[6,9,15] Overall, the SF-36 scores for pSS patients in our study were comparable to those mentioned in earlier literature.[8,10,15]

We observed more limitations in physical functioning in patients with sSS than in pSS patients. This is in contrast to the results described by Sutcliffe et al[7] and Tensing et al.[9] The latter studies were performed in smaller patient cohorts and mainly included patients with sSS with SLE as second autoimmune disease. The associated rheumatic disease in our sSS patients was more diverse (RA, SLE and other). RA patients are considered to be more restricted in physical functioning than SLE patients,[16] which might explain the difference in results. We, however, did not observe such a difference between sSS/RA and sSS/SLE patients; perhaps because of the relatively small sSS subgroups in our study.

Table 5. Logistic multivariate regression analyses for employment and receiving DC in SS patients.

Variable	Model 1		Adjusted for confounding	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Employment				
Bladder involvement	0.19 (0.05, 0.75)	0.017	0.20 (0.05, 0.81)	0.024
Oral moisturising gel use	0.32 (0.11, 0.94)	0.038	0.37 (0.12, 1.15)	0.084
NSAID use	0.30 (0.12, 0.81)	0.017	0.25 (0.09, 0.70)	0.008
Oral corticosteroids use	0.16 (0.04, 0.59)	0.006	0.14 (0.04, 0.56)	0.005
Comorbidity	0.13 (0.05, 0.36)	0.000	0.14 (0.05, 0.39)	0.000
Age at diagnosis, years	0.95 (0.92, 0.97)	0.000	0.97 (0.92, 1.02)	0.261
High level of education	4.39 (1.69, 11.44)	0.002	4.21 (1.59, 11.16)	0.004
Autoimmune thyroiditis			0.46 (0.09, 2.54)	0.376
Artificial tears use			0.50 (0.18, 1.37)	0.177
Age, years			0.97 (0.92, 1.02)	0.250
Receiving DC				
Number of EGM	1.37 (1.04, 1.80)	0.026	1.28 (0.96, 1.70)	0.099
Artificial saliva use	6.89 (1.92, 24.76)	0.003	6.21 (1.66, 23.18)	0.007
Antimalarial drug use	3.41(1.19, 9.74)	0.022	2.79 (0.94, 8.32)	0.065
Comorbidity	2.70 (1.08, 6.79)	0.034	2.73 (1.05, 7.11)	0.039
Age at diagnosis, years	0.93 (0.90, 0.97)	0.000	0.94 (0.90, 0.97)	0.000
Male gender	23.11 (4.40, 121.24)	0.000	32.21 (5.23, 198.42)	0.000
High level of education	2.86 (1.09, 7.50)	0.032	2.66 (1.00, 7.06)	0.050
Fatigue			3.33 (0.67, 16.57)	0.142
Skin involvement[a]			1.35 (0.41, 4.42)	0.625
Pilocarpine use			2.72 (0.76, 9.74)	0.124

[a] skin involvement other than cutaneous vasculitis.
CI, confidence interval; EGM, extraglandular manifestations; NSAIDs, non-steroidal anti-inflammatory drugs; UTI, urinary tract infections.

In our regression analyses, several demographic and clinical factors were found to be associated with HR-QoL. The unexplained variance probably reflects unmeasured, non-disease-related psychosocial factors such as self-esteem, support and coping strategies,[17] and other factors such as immunological parameters, delay in diagnosis and untreated or undiagnosed depression.[15] Interestingly, fatigue was an important explanatory variable for reduced physical and mental HR-QoL. This finding is in agreement with other studies.[5,9,18] Furthermore, the importance of fatigue in SS was underscored by the fact that the majority of patients with SS felt tired and 40% ranked fatigue as their most severe symptom. Fatigue should therefore be considered as an important treatment target.
Segal et al[19] demonstrated that psychological variables such as depression are determinants for fatigue, but only partly account for it. Since depression could be of im-

portance for our outcome measures as well, the use of antidepressants was scored in our population (9%). The regression analyses showed that antidepressants were a predictive factor for mental HR-QoL, as can be expected; but not for physical HR-QoL, employment or receiving DC.

We observed low employment and high disability rates in SS, which also have been reported for rheumatic diseases such as RA[17,20] and ankylosing spondylitis.[17] To our knowledge, these results have not previously been reported in SS patients.

A high level of education and comorbidity were the most significant predictors for having paid employment. One would expect, however, that fatigue and arthralgia would also have influenced the employment status. A possible explanation for the lack of this association could be that, with time, patients have gradually adapted their activities to these symptoms. This hypothesis is supported by the fact that only 10% of employed patients had a full-time job.

We found a higher frequency of EGMs (95%) compared with other studies.[8,12,15] This can partly be explained by the extended definition of EGMs used in this study. Interestingly, we found a higher frequency of Raynaud's phenomenon (43%), as compared with the study performed by Garcia-Carrasco et al (16%).[12] This may be explained by different weather circumstances in The Netherlands. The observed higher prevalence of lymphoproliferative disease (15 versus 2%) may be related to the use of parotid gland biopsies in the diagnostic work-up of our patients.[21] Parotid biopsies are more suited for (early) detection of lymphoproliferative disease than labial biopsies as mucosa associated lymphoid tissue and non-Hodgkin lymphomas are rarely found in labial glands.

Although the percentage of patients with EGMs did not differ between pSS and sSS patients, it should be noted that part of the EGMs in sSS patients could be attributed to the associated autoimmune disease and not only to SS. EGMs and EGM-related treatment were predictive for HR-QoL, employment and receiving DC. Therefore, there is a need for accurate follow-up and treatment aimed at EGMs.

The response rate of 83% in our study is very reasonable. As such, the risk of a sampling bias of certain categories of patients to be preferentially included in this study is considered negligible. Furthermore, we did not observe any significant differences for age, gender and pSS/sSS ratio between responders and non-responders. We, therefore, conclude that our results are representative for SS patients regularly attending a medical center specialised in SS patient care.

Since many SS patients suffer from reduced HR-QoL and are restricted in social and work-related activities, there is a great need for developing adequate treatment modalities to reduce SS-related complaints and to intervene in the progression of SS. Currently, no causal systemic treatment is available in SS and, therefore, only symptomatic treatment can be given. Recently, some studies reported good results of treatment with biologicals, especially anti-CD20 treatment.[22-25] Therefore, further development and evaluation of systemic treatment options should be stimulated.

CONCLUSION

SS has a large impact on HR-QoL, employment and disability as reflected by lower SF-36 scores and employment rates, and higher disability rates in SS patients as compared with the general Dutch population. Several demographical and clinical factors were associated with HR-QoL, employment and receiving DC. Physical functioning, bodily pain and general health were worse in sSS than in pSS patients.

ACKNOWLEDGEMENTS

We would like to thank Dr M Pompen and Dr E Ten Vergert for their expertise in the development of the questionnaire; Dr M Jalving for reading the manuscript and providing constructive criticism; Prof NK Aaronson and Mr CM Gundy of the Netherlands Cancer Institute and the Dutch Office of Statistics for providing us with age- and gender-matched normative data on HR-QoL, employment and DC; and also J Bulthuis-Kuiper and RPE Pollard for their assistance in analysing the data.

References

1 Hansen A, Lipsky PE, Dörner T. Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. Curr Opin Rheumatol 2005;17:558-65.

2 Fox RI. Sjögren's syndrome. Lancet 2005;366:321-31.

3 Mitsias DI, Kapsogeorgou EK, Moutsopoulos HM. Sjögren's syndrome: why autoimmune epithelitis? Oral Dis 2006;12:523-32.

4 Boonen A, Rasker JJ, Stucki. The international classification for functioning, disability and health. A challenge and a need for rheumatology. Clin Rheumatol 2007;26:1803-8.

5 Bjerrum K, Prause JU. Primary Sjögren's syndrome: a subjective description of the disease. Clin Exp Rheumatol 1990;8:283-8.

6 Strombeck B, Ekdahl C, Manthorpe R, et al. Health-related quality of life in primary Sjögren's syndrome, rheumatoid arthritis and fibromyalgia compared to normal population data using SF-36. Scand J Rheumatol 2000;29:20-8.

7 Sutcliffe N, Stoll T, Pyke S, et al. Functional disability and end organ damage in patient with systemic lupus erythematosus (SLE), SLE and Sjögren's syndrome (SS) and primary SS. J Rheumatol 1998;25:63-8.

8 Champey J, Corruble E, Göttenberg JE, et al. Quality of life and psychological status in patients with primary Sjögren's syndrome and sicca symptoms without autoimmune features. Arthritis Rheum 2006;55:451-7.

9 Tensing EK, Solovieva SA, Tervahartiala T, et al. Fatigue and health profile in sicca syndrome of Sjögren's and non-Sjögren's syndrome origin. Clin Exp Rheumatol 2001;19:313-6.

10 Bowman SJ, Booth DA, Platts RG. Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. Rheumatology 2004;43:758-64.

11 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American European Consensus Group. Ann Rheum Dis 2002;61:554-8.

12 Garcia-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjögren's syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine 2002;81:270-80.

13 Ramos-Casals M, Font J, Garcia-Carrasco M, et al. Primary Sjögren's syndrome: hematologic patterns of disease expression. Medicine 2002;81:281-92.

14 Aaronson NK, Muller M, Cohen PD, et al. Translation, validation and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51:1055-68.

15 Belenguer R, Ramos-Casals M, Brito-Zeron P, et al. Influence of clinical and immunological parameters on the health-related quality of life of patients with primary Sjögren's syndrome. Clin Exp Rheumatol 2005;23:351-6.

16 Benitha R, Tikly M. Functional disability and health-related quality of life in South Africans with rheumatoid arthritis and systemic lupus erythematosus. Clinical Rheumatol 2007;26:24-9.

17 Chorus AM, Miedema HS, Boonen A, et al. Quality of life and work in patients with rheumatoid arthritis and ankylosing spondylitis of working age. Ann Rheum Dis 2003;62:1178-84.

18 Barendregt PJ, Visser MR, Smets EM, et al. Fatigue in primary Sjögren's syndrome. Ann Rheum Dis 1998;57:291-5.

19 Segal B, Thomas W, Rogers T, et al. Prevalence, severity, and predictors of fatigue in subjects with primary Sjögren's syndrome. Arthritis Rheum 2008;59:1780-7.

20 Verstappen SM, Boonen A, Bijlsma A, et al. Working status among Dutch patients with rheumatoid arthritis: work disability and working conditions. Rheumatology 2005;44:202-6.

21 Pijpe J, Kalk WW, van der Wal JE, et al. Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. Rheumatology 2007;46:335-41.

22 Vauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007;57:310-7.

23 Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005:52:2740-50.

24 Pijpe J, van Imhoff, Vissink A, et al. Changes in salivary gland immunohistology and function after rituximab monotherapy in a patient with Sjögren's syndrome and associated MALT lymphoma. Ann Rheum Dis 2005;64:958-60.

25 Meijer JM, Pijpe J, Bootsma H, et al. The future of biologic agents in the treatment of Sjögren's syndrome. Clin Rev Allergy Immunol 2007;32:292-7.

Chapter 3

Management of Sjögren's syndrome

Petra M Meiners[1], Jiska M Meijer[1], Arjan Vissink[1], Hendrika Bootsma[2]

Departments of [1]Oral and Maxillofacial Surgery and [2]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, The Netherlands

This chapter is an edited version of:
Chapter 12 Management of Sjögren's syndrome
In: Weisman, M.H., M.E. Weinblatt, J.S. Louie, R. van Vollenhove (eds). Targeted treatment of rheumatic diseases. Saunders, 2010: 133-55

INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune inflammatory disorder of exocrine glands. It particularly affects the lacrimal and salivary glands. Dry mouth and dry eyes are frequently the presenting symptoms. Extraglandular manifestations, for example, arthritis and polyneuropathy can also be present (table 1). In addition, many SS patients report functionally limiting chronic fatigue.

SS can be a primary idiopathic condition of unknown aetiology (primary Sjögren's syndrome, pSS). SS may also occur in the presence of another autoimmune disorder such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, or mixed connective tissue disease. In these cases the condition is designated as secondary Sjögren's syndrome (sSS). The estimated prevalence of SS in the general population is between 0.5 and 1%, which makes SS, after RA, the most common systemic autoimmune disease. In RA, the prevalence of SS is around 30%, and 20% of patients with SLE fulfill the criteria for sSS. SS is more frequent in women (female-to-male ratio, 9:1). Furthermore, SS is associated with organ-specific autoimmune diseases such as autoimmune thyroid disease, primary biliary cirrhosis, and autoimmune gastritis. This underscores the autoimmune nature of the disease.[1,2] Like other rheumatologic conditions, SS exerts a major impact on patients' health-related quality of life (HR-QoL). Apart from the symptoms mentioned earlier, patients may be restricted in their activities and their participation in society, resulting in reduced HR-QoL and impaired socio-economic status.[3]

Because patients have concomitant oral, ocular and systemic medical problems, the management of the patient with SS should ideally involve a multidisciplinary team of health care practitioners with good lines of communication between them. In a multidisciplinary team with a specialised rheumatologist, oral and maxillofacial surgeon, ophthalmologist, pathologist, haematologist, dentist and oral hygienist, SS patients can get the care they need. It is important that 1 physician, usually the rheumatologist, has overall responsibility for the care of the patient. The strategy followed at the University Medical Center Groningen, The Netherlands is given in figure 1.

Although there is as yet no curative or causal treatment for SS, various supportive and palliative treatment options are available, and targeted approaches (biological disease-modifying antirheumatic drugs (DMARDs)) are in development or currently being tested in phase I or phase II trials. This chapter presents and discusses the management of both glandular and extraglandular manifestations of SS (including mucosa-associated lymphoid tissue (MALT) lymphoma), and discusses prospects focussing on better understanding of the progression and more effective treatment of SS.

Table 1. Extraglandular manifestations in primary Sjögren's syndrome.[3,14,94]

Anatomic system	Findings	%*
Constitutional symptoms	Fatigue	80
	Fever	5
	Lymphadenopathy	15
Joints/muscles	Articular involvement	50
	Tendomyalgia	40
	Myositis	2
Skin	Raynaud's phenomenon	40
	Cutaneous vasculitis	15
	Skin involvement other than cutaneous vasculitis	5
Endocrine	Autoimmune thyroiditis	10
Respiratory tract	Pulmonary involvement	25
	Serositis	2
Gastrointestinal tract	Esophageal involvement	5
	Autoimmune hepatitis	10
	Acute pancreatitis	1
Nervous system	Peripheral neuropathy	10
	CNS involvement	2
Urogenital tract	Renal involvement	10
	Bladder involvement	15
Haematology	Thrombocytopenia	2
	Lymphoproliferative disease	5

*% differ greatly between studies.
CNS, central nervous system.

CLASSIFICATION AND DIAGNOSIS OF SJÖGREN'S SYNDROME

Many classification criteria for SS have been suggested. Presently, the American-European Consensus Group (AECG) criteria, which were proposed in 2002, are the most widely accepted and validated criteria (table 2). These criteria combine subjective symptoms of dry eyes and dry mouth with objective signs of keratoconjunctivitis sicca and xerostomia.[4]

The subjective ocular and oral symptoms are obtained by history taking. Two tests are used to objectify reduced tear production. In the Schirmer's test a piece of filter paper is placed laterally on the lower eyelid, which results in wetting due to tear production. If less than 5 mm of paper is wetted after 5 minutes, the test result is positive (figure 2). In the Rose Bengal test, dye stains devitalised areas of the cornea and conjunctiva which can be scored using a slit lamp. A Rose Bengal score ≥4 according to the Van Bijsterveld scoring system is considered abnormal. Instead of Rose Bengal stain, lissamin green can be used, which shows comparable results but is less painful. An additional test that is not

Table 2. Revised American-European Consensus Group criteria and revised rules for classification for Sjögren's syndrome.[4]

I. Ocular symptoms: a positive response to at least 1 of the following questions:
   1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   2. Do you have a recurrent sensation of sand or gravel in the eyes?
   3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least 1 of the following questions:
   1. Have you had a daily feeling of dry mouth for more than 3 months?
   2. Have you had recurrently or persistently swollen salivary glands as an adult?
   3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs-that is, objective evidence of ocular involvement defined as a positive result for a least 1 of the following 2 tests:
   1. Schirmer's I test, performed without anaesthesia (≤5 mm in 5 minutes)
   2. Rose Bengal score or other ocular dye score (e.g., Lissamin green; ≥4 according to Van Bijsterveld's scoring system)

IV. Histhopathology: in minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least 1 of the following diagnostic tests:
   1. Unstimulated whole salivary flow rate (≤ 1.5 mL in 15 minutes)
   2. Parotid sialography showing delayed uptake, reduced concentration and/or delayed excretion of tracer
   3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:
   1. Antibodies to Ro/SSA or La/SSB antigens, or both

Revised rules for classification

For primary SS
In patients without any potentially associated disease, primary SS may be defined as follows:
a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, VI)
c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

For secondary SS
In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria:
Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficienty disease (AIDS)
Pre-existing lymphoma
Sarcoidosis
Graft versus host disease
Use of anticholinergic drugs (since a time shorter that 4-fold the half life of the drug)

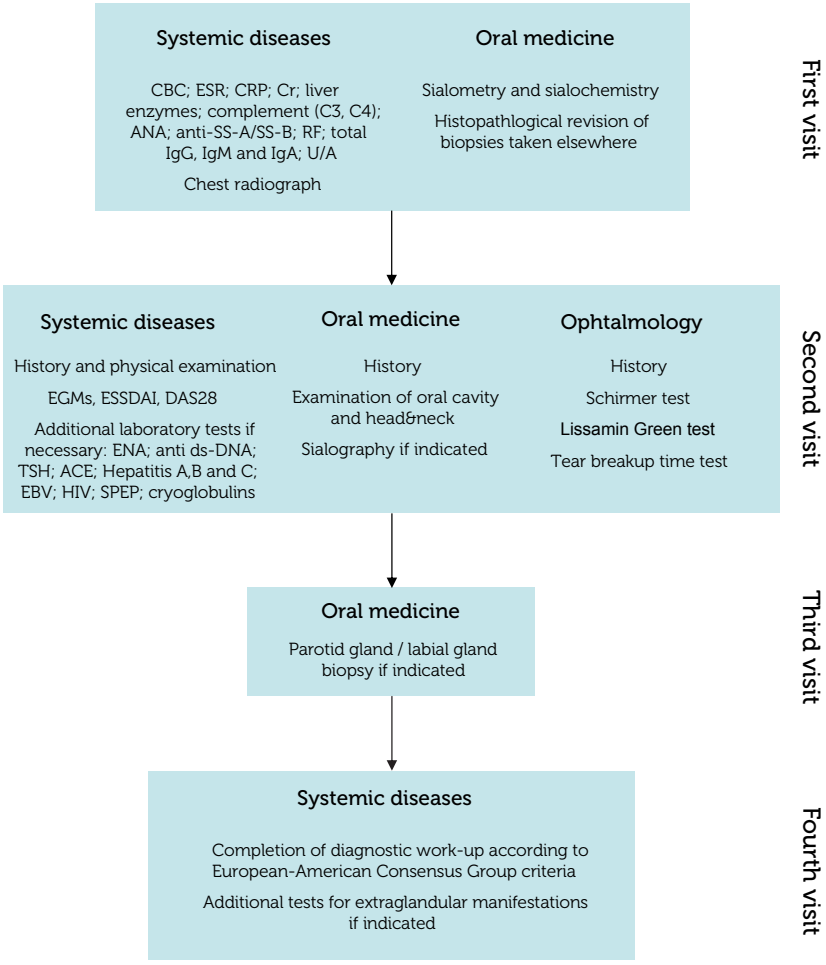

Figure 1. Diagnostic work-up strategy for patients referred under clinical suspicion of SS to the University Medical Center Groningen, The Netherlands. The referral may come from dentists, general practitioners, or other specialists. Before the first visit patients receive written information about the diagnostic procedure followed at our institution. ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; CBC, complete blood cell count; Cr, creatinine; CRP, C-reactive protein; ds-DNA, double-stranded DNA; DAS28, disease activity score 28; EBV, Epstein-Barr virus; EGMs, extraglandular manifestations; ENA, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; ESSDAI, Eular Sjögren's syndrome disease activity index; HIV, human immunodeficiency virus; RF, rheumatoid factor; SPEP, serum protein electrophoresis; TSH, thyroid stimulating hormone; U/A, urinalysis.

accepted as diagnostic technique for SS, but provides a global assessment of the function of the tear film is the tear break-up time test. This test is performed by measuring break-up time and tear osmolarity after instillation of fluorescein. An interval of less than 10 seconds is considered abnormal.

To confirm the diagnosis of SS histopathologically, usually a biopsy from a labial salivary gland is taken. This should show focal lymphocytic sialoadenitis with a focus score of ≥ 1 (a focus is defined as an accumulation of 50 or more lymphocytes per 4 mm^2).[5] Recently it has been shown that parotid biopsy might serve as a proper alternative for labial biopsy in the diagnosis of SS (figure 3). Its morbidity is less than that of labial salivary gland biopsy. In addition, MALT/non-Hodgkin's lymphoma (NHL) pathology is easier to detect, because the labial glands are less commonly affected by MALT/NHL than the parotid glands.[6] Moreover, in contrast to a labial biopsy, parotid biopsies can be used to monitor various treatment methodologies since the same gland can be biopsied more than once.

Currently, 3 diagnostic tests can be used to objectify salivary gland involvement, other than histopathology. The most commonly applied objective salivary gland diagnostic test is measuring the flow rate of unstimulated, whole saliva. Unstimulated whole salivary flow rate is a very useful indicator of salivary function and oral wetness. The patient is asked to expectorate once, then to collect all saliva into a graduated container. After 15 minutes, the volume of saliva is measured. These sialometric tests should be routinely performed regardless of whether the patient does or does not complain of oral disease, allowing later comparisons if the patient develops subjective oral dryness or presents with other clinical signs of salivary dysfunction.[7] For research purposes, or if more specific functional information is required for a particular gland, individual gland collection techniques can be used. Collection of glandular saliva is not difficult but requires specialised equipment (e.g., a Lashley cup) and takes more time to perform. Other tests to evaluate salivary gland involvement are sialography and salivary gland scintigraphy. Sialography is the radiographic imaging of the salivary duct system through retrograde infusion of an oil- or water-based contrast fluid (figure 4).[8] Sialography has a low morbidity and is well accepted by patients.[9] The main sialographic characteristic of SS is a diffuse collection of contract fluid at the terminal acini of the ductal tree, termed sialectasia.[10,11] Sialography has a high diagnostic accuracy. Finally, patients with SS demonstrate decreased uptake and release of technetium Tc 99m pertechnetate on scintigraphy.[12] At present, efforts are made to improve the diagnostic accuracy of scintigraphy.[13]

Approximately 80% of patients with SS display antinuclear antibodies (ANAs) and about 40 to 60% of them have antibodies against anti-Ro/SSA. This autoantibody is considered to be the most specific serologic marker for SS, even though it is also found in 25 to 35% of patients with SLE or other autoimmune connective-tissue disorders, and in about 5% of healthy subjects. Besides the presence of antibodies to Ro/SSA or La/SSB other laboratory blood studies are helpful in patients suspected of SS. The presence of nonspecific

markers of autoimmunity, such as ANAs, rheumatoid factor (RF), elevated immunoglobulins (particularly immunoglobulin G (IgG)), and elevated erythrocyte sedimentation rate (ESR) are important contributors to the definitive diagnosis of SS.[14]

Diagnostic work-up

There is a large diversity in the initial clinical manifestation in patients with SS, and these manifestations are not always present at the same time. Therefore, physicians and dentists sometimes treat each symptom individually, unaware of an underlying systemic disease. In addition, patients with SS were frequently misdiagnosed in the past because their symptoms were considered minor or vague or mimicked those of other diseases. Consequently, delayed diagnosis in SS patients is frequent.

An extensive delay in diagnosis can affect the patient's well-being if for no other reason than because of the anxiety that accompanies an undiagnosed illness. Early, accurate diagnosis of SS (figure 1) can help prevent or ensure adequate treatment of many of the complications associated with the disease, and may contribute to prompt recognition and treatment of serious systemic complications of SS.[15]

GLANDULAR MANIFESTATIONS: EXOCRINE DYSFUNCTION

Patients with SS have symptoms related to a diminished function of the exocrine glands, in particular, the lacrimal and salivary glands, although SS may also affect the glands in the upper respiratory tract, skin and vagina.

Ocular manifestations

Dryness of the eyes is the most prominent ocular manifestation of SS, and one fourth of SS patients report eye dryness as the first complaint.[16] It results in sensations of itching, burning, dryness, soreness and grittiness. Other ocular symptoms that may arise from ocular dryness are photosensitivity or photophobia, erythema, eye fatigue, decreased visual acuity, discharge in the eyes, and the sensation of a film across the visual field. These symptoms may be exacerbated by low humidity environments, such as air-conditioned or centrally heated buildings or dry climates, or exposure to irritants such as dust and cigarette smoke.

Physical examination reveals chronic irritation and destruction of both corneal and bulbar conjunctival epithelium (keratoconjunctivitis sicca) due to insufficient tear secretion. Accumulation of thick rope-like secretions along the inner canthus may be the result of decreased tear film and abnormal mucus component. At times, desiccation causes small superficial erosions of the corneal epithelium; in severe cases, slitlamp examination reveals filamentary keratitis, marked by mucus filaments that adhere to damaged areas of the corneal surface. Progressive keratitis can result in loss of vision. Blepharitis,

which is the inflammation and infection of the meibomian glands of the eyelid, is a common problem in patients with dry eyes, and conjunctivitis as a result of secondary infection with *Staphylococcus aureus* may also occur. Enlargement of the lacrimal glands is rare and should prompt a work-up for MALT. Ocular complications that may arise from SS include corneal ulceration, vascularisation, opacification, and rarely perforation.[15]

Oral manifestations

Autoimmune destruction of the salivary glands results in oral symptoms that accrue primarily as result of salivary gland hypofunction and are due to the long-term effects of a decrease in oral fluids on mucosal hydration and oral function.

Loss of salivary gland function is already prominent in early onset SS. The submandibular and sublingual salivary glands, which are the most active glands under resting condition, are among the first glands to be involved in SS, whereas the parotid gland, the most active gland when stimulated, appears the last salivary gland to be affected. Patients with SS with long disease duration are characterized by severely reduced secretions of the parotid, submandibular and sublingual glands. This results is a typical symptomatic pattern: in early SS, the sensation of dry mouth (xerostomia) is often present predominantly at rest and during the night. Over time, as the disease develops, the dryness is also present during the day and finally it gives rise to difficulties in chewing and swallowing food.[7]

Reduction in saliva production (figure 5) may also lead to difficulties in speaking and be related to burning sensations in the mouth. A diminished ability to taste foods and having problems with smell or a mucosa that is sensitive to spicy or coarse foods, are frequently mentioned symptoms. This limits the patient's enjoyment of meals and may compromise his or her nutrition.[17,18] Most patients carry bottles of water or other fluids with them at all times to aid speaking and swallowing and for their overall oral comfort, and many patients report about the decrease in their HR-QoL since the advent of oral dryness.

Patients with advanced salivary gland hypofunction as a result of SS have obvious signs of mucosal dryness (figure 6).[19,20] The lips often appear cracked, peeling and atrophic. They may even appear furrowed or pebbled, like dry soil in an arid climate. The buccal mucosa may be pale and corrugated in appearance, and the tongue may be smooth and reddened, with loss of some of the dorsal papillae or may have a fissured appearance. There is often a marked increase in erosion and dental caries. The decay may be progressive, even in the presence of vigilant oral hygiene. With diminished salivary output, there is a tendency for greater accumulations of food debris at the so-called smooth surfaces and cervical regions, especially where recession has occurred (figure 7). Patients with a dry mouth as a result of SS also experience an increase in oral infections, particularly mucosal candidiasis (figure 8).[19,21] The patient may present with red, erythematous patches on the oral mucosa, for example beneath dentures, or it may appear as white, curd-like mucocutaneous lesions on any surface (thrush), or the patient may complain of a burning sensation of the tongue or other intraoral soft tissues. Fungal

lesions of the corners of the mouth (angular cheilitis) may also occur more frequently in patients with SS (see figure 6C).

Enlargement of the salivary glands

Enlargement of the salivary glands is seen frequently, in particular of the parotid and submandibular glands. Enlargement is generally due to the presence of an autoimmune inflammatory process in these glands. In the parotid glands this inflammation process can be seen unilaterally but is most often present on both sides. Furthermore, salivary gland enlargement can be chronic or episodic. Stasis of saliva, which may occur due to distortion and narrowing of ducts, can result in secondary infection in cystic areas, leading to further swelling of the glands. Thirdly, glandular enlargement may be due to lymphoma development within, in most cases, the parotid gland. Most often these are MALT lymphoma but other NHLs may also develop.

Normally, palpation of the salivary glands is painless. Saliva can be "milked" from each major gland by compressing the glands, with bimanual palpation, and by pushing the fluid contained within them to the gland orifices. The expressed saliva should be clear, watery, and copious.

Diffuse swollen glands that are painful on palpation are indicative of infection or acute inflammation. Viscous saliva or scant secretions suggest chronically reduced function. A cloudy exudate may be a sign of bacterial infection. In these cases, there may be mucoid accretions and clumped epithelial cells, which account for the cloudy appearance of saliva. The exudate should be cultured if it does not appear clear, particularly in the case of an enlarged gland. Occasionally, a purulent secretion is observed, which makes the diagnosis bacterial sialadenitis obvious.

Because the incidence of NHL lymphomas, including MALT lymphomas of the salivary glands, is about 40 times increased in SS patients, physicians should be alert for painless nodular masses, in particular in the parotid gland. Especially SS patients with risk factors for progression to lymphoma, namely those with persistent salivary gland enlargement, low levels of C4, and monoclonal cryoglobulinemia, should be monitored closely.[22,23]

Additional dry surfaces

Dryness is not restricted to the eyes and mouth but also occurs at mucosal surfaces in the upper and lower airways, frequently leading to dryness of the nose, throat, and trachea resulting in persistent hoarseness and a chronic, nonproductive cough. Patients may also experience dermal dryness, and in female SS patients, desiccation of the vagina and vulva may result in dyspareunia and pruritis.[15]

PATIENT CASE

This case describes a 35-year-old female with a 3-year history of pSS. The diagno-

sis had initially been confirmed by the absence of saliva secretion (unstimulated and stimulated), an abnormal sialography result, low Schirmer's test values, an abnormal lissamin green test, anti-SSA and anti-SSB antibodies, and a positive labial biopsy. During follow-up she developed a progressive, bilateral swelling of the parotid glands (figure 9) and the submandibular lymph nodes. Other signs she developed were buccal petechiae and bilateral lower limb purpura. Laboratory examination revealed low complement C4 levels (0.05 g/L, normal range 0.1-0.4 g/L), a worsening of her pre-existent hypergammaglobulinemia (IgG 19.6 g/L, normal range 7.0-16.0 g/L) and an elevated RF (153 kIU/L, normal <11 kIU/L). These results raised the suspicion that she had developed a malignant lymphoma. Magnetic resonance imaging showed pronounced enlargement of the parotid glands with multiple cystic lesions. In addition, there were several enlarged cervical lymph nodes. To confirm the diagnosis, an excision biopsy of an enlarged lymph node and a parotid gland biopsy were performed.
Histopathological and immunohistochemical examination of both biopsies showed an MALT lymphoma. The B-cells were monoclonal. Further staging investigations were not performed because the patient was pregnant at the time. During her pregnancy the patient was treated with 15 mg of prednisone once a day. After delivery, she was treated with anti-CD20 monoclonal antibodies (rituximab) because of increasing swelling of the parotids, a larger number of vasculitic lesions and progression of the MALT lymphoma. Treatment led to a reduction in size of the parotid glands and lymph nodes, improvement of the vasculitic lesions and increasing complement C4 levels.

MANAGEMENT OF GLANDULAR MANIFESTATIONS

In general, adequate explanation of the condition, including use of patient information brochures, will help in empowering patients to participate in their own care. Furthermore, various preventive measures and symptomatic treatments can be given in SS. It is possible that a single treatment modality may help; it is also possible that a combination of them may be necessary. Management strategies are provided in tables 3 and 4.

Management of ocular manifestations

Dry eye disease might be a sight threatening problem in SS patients, and many patients are suffering from eye complaints all day. Treatment of ocular manifestations in these patients is difficult and often does not lead to satisfactory results.
The most widely used therapy for dry eye disease is tear substitution by topical artificial tears, to increase humidity at the ocular surface and to improve lubrication. However, the use of artificial tears has obvious limitations. Natural tears have a complex composition of water, salts, hydrocarbons, proteins, and lipids, which artificial tears cannot completely substitute. In addition, the integrity of the 3-layered lipid, aqueous, and mucin structure,

Table 3. Management strategies for ocular manifestations of Sjögren's syndrome.

Strategy	Approach	Description
Preventive measures	Avoidance exacerbating factors	• Avoiding low humidity atmospheres such as air-conditioned stores, centrally heated houses, airplanes, windy locations • Avoiding irritants such as dust and cigarette smoke • Avoiding activities that provoke tear film instability (e.g., prolonged reading or computer use)
	Avoidance of drugs that may worsen sicca symptoms	• Caution when using antidepressants, antihistamines, anticholinergics, antihypertensives, neuroleptics
	Treatment of other medical conditions that result in dry eyes	• Eyelid abnormalites (e.g., ectropion), meibomean gland disease
Symptomatic treatment	Tear substitution therapy	• Low viscous eye drops (Schirmer ≤5 mm/5 minutes) and high mucus secretions in the cul du sac • High viscous eye drops (Schirmer >5 mm/5 minutes) and low mucus secretions in the cul du sac • Opthalmic gels and ointments (at night)
	Blepharitis	• Daily eyelid rubs with warm water and diluted baby shampoo • Topical antibiotics if indicated
	Add mucolytic agents for mucus secretions/sticky eyes/ mucus filaments in eye examination	• N-acetylcysteine 5% eye drops (2-3 times daily)
	Tear retention measures	• Use of air moisturisers • Moisture glasses • Lacrimal punctum occlusion (moderate to severe dry eyes)
	Topical immunomodulatory agents	• Topical nonpreserved corticosteroids (e.g., dexamethason 0.1% eyedrops 2 times daily; taper dose or discontinue drops based on clinical findings and eye pressure)
Tear stimulation	Systemic parasympathomimetic secretogogues	• Pilocarpine (5-7.5 mg, 3-4 times/day) • Cevimeline (30 mg, 3 times/day)
Treating underlying disorder	Systemic anti-inflammatory or immune modulating therapies to treat the autoimmune exocrinopathy of Sjögren's syndrome	• Rituximab

which is vital to the effective functioning of the tear film, cannot be reproduced by these artificial components. The majority of tear substitutions is not preservative free. Because many preservatives contain chemical substances that may damage the tear film stability and the cornea epithelium, use of preservative-free artificial tears is strongly recommended. Patients are advised not to use these tear substitutes as frequently as they want, because the substitutes dilute the small amount of natural tears that are still present, and because of the potential harmful effects of preservatives as mentioned above (table 3).

Preventive measures

First of all, factors that can cause exacerbation of ocular symptoms should be avoided whenever possible. This includes windy or low-humidity environments and exposure to irritants such as dust and cigarette smoke. Patients can be instructed how to increase humidity in their own surroundings by installing room humidifiers. Activities that provoke tear film instability, such as prolonged reading or computer use should also be avoided or modified (e.g., taking regular breaks from reading or computer use, and lowering the computer monitor in a way that the gaze is directed downward).[24]

Several medical conditions and medications can result in keratoconjunctivitis sicca. Dry eyes can be caused by amyloidosis, inflammation (chronic blepharitis or conjunctivitis, pemphigoid, or Stevens-Johnson syndrome), neurologic conditions that impair eyelid or lacrimal gland function, sarcoidosis, toxicity (burns or drugs), and a variety of other conditions (corneal anaesthesia, blink abnormality, hypovitamininosis A, eyelid scarring, or trauma). Antidepressants, antihistamines, anticholinergics, antihypertensives (diuretics, ß-blockers) and neuroleptics may cause dry eyes as well.[15] The pathological conditions should be ruled out or otherwise be promptly treated, and the use of drugs that may worsen sicca symptoms should be avoided.

Symptomatic treatment

Substitution therapy is the main treatment modality. Patients with a Schirmer's test of 5 mm/5 minutes or less and high mucus secretions in the cul du sac are treated with low-viscosity eye drops. In patients with a Schirmer's test more than 5 mm/5 minutes, with no or little mucus in the cul du sac, high-viscosity eye drops are prescribed. Patients are advised to use the drops 3 times a day, with a maximum of 6 times a day. Patients can test several different drops to determine which one is most suitable for their own individual needs. Opthalmic gels and ointments may be used at night. Highly viscous drops, ophthalmic gels, and ointments last longer, but they may cause visual blurring. Blepharitis may worsen by the use of artificial tears, especially those with high viscosity or those containing preservatives. Treatment of blepharitis consists of cleansing of the eyelids (using warm water and diluted baby shampoo), and topical antibiotics, if needed. If the patient reports mucus secretions in the eyes or sticky eyes, a mucolytic agent, such as acetylcysteine 5% eye drops can be added to the medication, used 2 to 3 times

a day. When successful, taper the dose; when no effect is seen, application of these drops should be discontinued. Mucolytic eye drops can also be prescribed when mucus filaments are found on eye examination.

Topical nonpreserved corticosteroids (e.g., dexamethason drops) can be used to suppress the associated inflammatory process. Their use should be restricted, because of their severe side effects, such as glaucoma, cataract and increased risk of secondary infections and epithelial defects.[24] Therefore their use should be either discontinued or the dose tapered as soon as possible, based on clinical findings and eye pressure.

To prevent drying out of the eyes, occluding glasses or moisture glasses can be tried. Tear preservation can also be achieved by closing of the orifice of the lacrimal duct, lacrimal punctum occlusion, a relatively common nonpharmacologic treatment for dry eye disease. Punctum occlusion can be achieved by temporary plugs, or by a permanent surgical procedure. This treatment can improve the quality and the quantity of the aqueous component of the tear film, relieving symptoms and signs of dry eye, making patients more comfortable and reducing the need for frequent administration of artificial tears. Nevertheless, these claims are controversial. Some authors have reported disadvantages to this technique including extrusion or loss of the plug, pruritis, discomfort, abrasion of the conjunctiva and cornea, tear overflow (epiphora), inflammation of the lacrimal duct (canaliculitis) and pyogenic granuloma. Furthermore, punctal occlusion may result in decreased tear production and clearance, and diminished ocular surface sensation. Therefore, most authors reserve this method for moderate to severe dry eyes and only in those patients in whom frequent use of unpreserved artificial tears and lubricants remains insufficient.[25]

Systemic tear stimulation

Two secretagogues, pilocarpine[26,27] and cevimeline[28,29] have been approved by the United States Food and Drug Administration for the treatment of dry mouth, and these drugs are also found to be effective for dry eye disease. Both drugs induce a transient increase in lacrimal and salivary output, and decrease their feeling of ocular and oral dryness in patients who have residual functional lacrimal and salivary gland tissue. These drugs will be discussed in more detail in the management of oral manifestations section.

Systemic anti-inflammatory or immune-modulating therapies

In general, immune modulating or immunosuppressive treatment has been disappointing for the glandular manifestations of SS. However, recently, promising results have been reported with biological DMARDs. Relief of ocular and oral symptoms, fatigue, and other extraglandular manifestations was seen after treatment with anti-CD20 (rituximab), assessed with both subjective as well as objective measures.[30-35] These medications are discussed in the section on biological DMARDs.

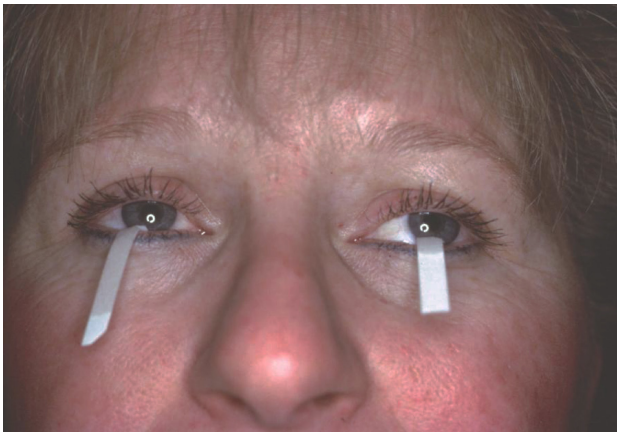

Figure 2. The Schirmer's test can be used to assess lacrimal function in patients suspected of having SS. In SS the tear secretion of both eyes is reduced (< 5 mm/5 minutes). The case presented shows reduced tear secretion in the left eye and a normal function in the right eye (patients with SS usually show similar changes in both eyes).

Management of oral manifestations

Preventive and general measures for oral complications

Because individuals with Sjögren's syndrome are at risk for a variety of oral complications, preventive measures are of great importance, in which the dentist plays a leading role.

SS patients will require more frequent dental visits (usually every 3 to 4 months) and must work closely with their dentist and dental hygienist to maintain optimal dental health. Visits might be schedueled in alternating order: dentist–dental hygienist–dentist–dental hygienist. Prosthesis-wearing patients should have their prosthesis-bearing mucosal regions evaluated frequently (every 3 to 4 months) to help identify the early onset of oral mucosal lesions and infections. In dentate SS patients, periodic radiographs should be taken more frequently than in healthy individuals, to follow-up on previous carious lesions and to trace new ones.

It is essential that SS patients maintain meticulous oral hygiene. Proper oral hygiene includes tooth brushing, flossing, the use of interproximal plaque removing agents, and the use of mouth rinses. Interdental brushes and mechanical toothbrushes are helpful for those with oral-motor or behavioural complications. Regular brushing of the tongue with a toothbrush or a tongue scraper is also recommended. The team of oral-health professionals must play an important role in providing guidance (clinical instructions, written instructions) to the SS patient so that he or she is given every opportunity to prevent the onset of the common side effects of salivary hypofunction.

Furthermore, the use of topical fluorides in a patient with salivary gland hypofunction is absolutely critical to control dental caries.[36] There are many different fluoride therapies

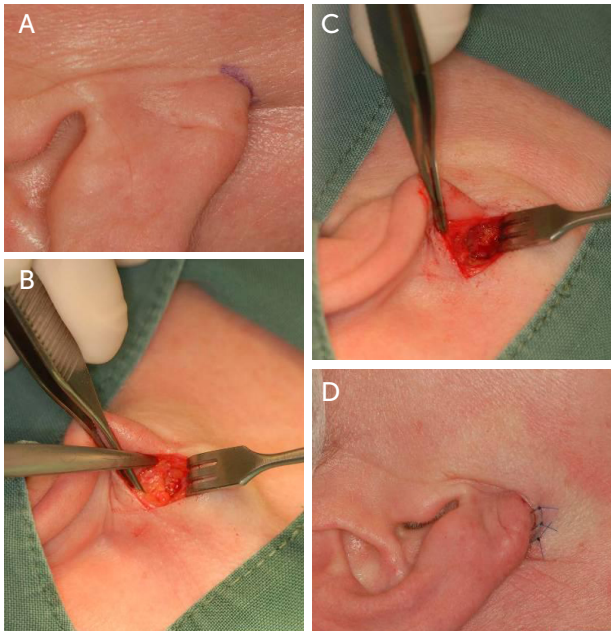

Figure 3. A parotid gland biopsy is performed under local anaesthesia, according to the technique described by Kraaijenhagen (1975). (A) the area to be incised is marked, B) the fibrous capsule surrounding the parotid gland is visualized, (C) the capsule is openened and a small amount of superficial parotid gland tissue is removed,(D) the skin is closed.

available, from low-concentration, over-the-counter fluoride rinses, to more potent highly concentrated prescription fluorides (e.g., 1.0% sodium fluoride). These are applied by brush or in a custom carrier. Oral health care practitioners may also use fluoride varnishes. The dosage chosen and the frequency of application (from daily to once a week) should be based on the severity of the salivary hypofunction and the rate of caries development.[37-39] A 5000-PPM fluoridated toothpaste, used twice daily, has been recommended for high-caries-risk patients with salivary dysfunction.[36]

When salivary function is compromised, the normal process of tooth remineralisation is interrupted. This enhances demineralisation and the consequent loss of tooth structure. Remineralising solutions and fluorides (toothpaste, mouth rinse, neutral fluoride gel) should be used to alleviate some of these changes.[40]

Patients should be counselled to follow a diet that avoids cariogenic foods (especially fermentable carbohydrates) and beverages. The implementation of meticulous oral hygiene procedures after each meal is critical to help reduce the risk of developing new and recurrent carious lesions. Chronic use of alcohol and caffeine can increase oral dryness and should be minimised. Nonfermentable dietary sweeteners, such as xylitol, sorbitol, aspartame or saccharine are recommended, whenever possible.[41] Polyols such

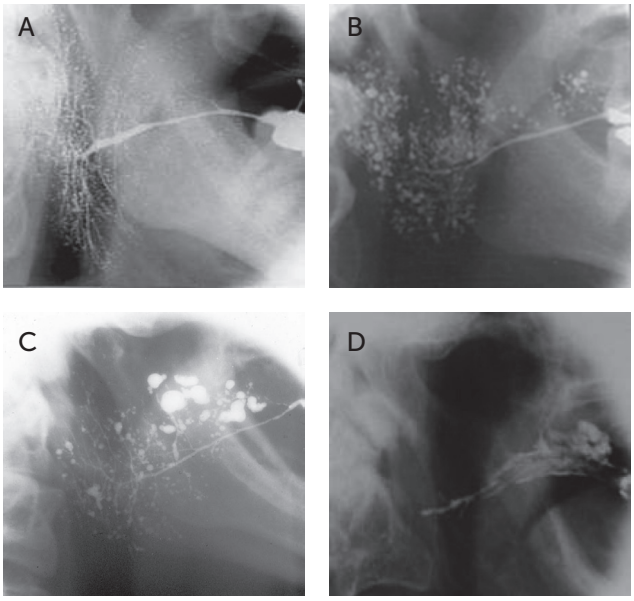

Figure 4. Sialography showing dilated and distorted ducts (sialectasis). Stadia of sialectasia: (A) punctate (<1 mm), (B) globular (uniform, 1-2 mm), (C) cavitary (coalescent, >2 mm), (D) destructive (no structure visible).

as xylitol, are considered to be anticariogenic because they decrease acid fermentation by *Streptococcus mutans.*[42]

Low-humidity atmospheres and irritants should be avoided whenever possible.

Local salivary stimulation

Dry mucosal surfaces, difficulty wearing dentures, accumulation of plaque and debris on surfaces normally cleansed by the mechanical washing action of saliva, difficulty speaking, tasting, and swallowing may all benefit from several techniques available to stimulate salivary secretions. These techniques work only if there are remaining viable salivary gland cells that are amenable to stimulation. In patients with long-term SS, the acinar fluid-producing cells may have already undergone atrophy. The atrophied tissue is generally replaced by non-fluid-producing connective tissue cells, which, clearly, do not respond to stimulation techniques.

Masticatory stimulatory techniques are the easiest to implement and have few side effects. The combination of chewing and taste, as provided by sugar free gums or mints, can be very effective in relieving symptoms for patients who have remaining salivary function. Special gum bases have been developed for patients with dry mouth because regular chewing gums are often too sticky to handle by dry mouth patients.

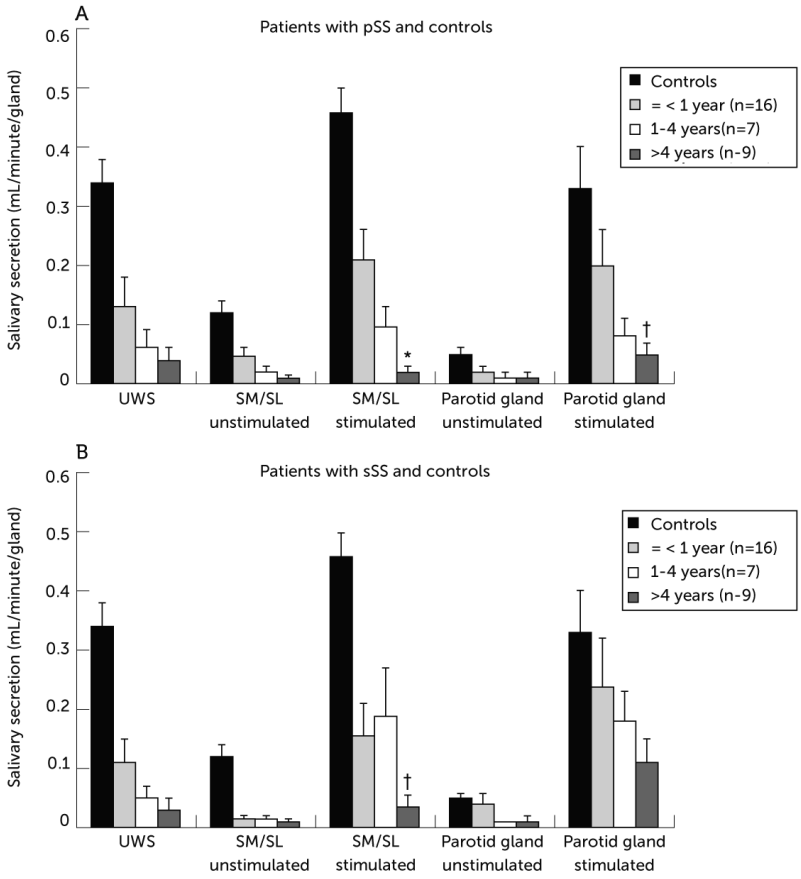

Figure 5. Relation between disease duration, that is, the time from first complaints related to oral dryness until referral, and mean salivary flow rates (mean±SEM). UWS, unstimulated whole salivary flow rate; SM/SL, submandibular/sublingual saliva. (From Pijpe J, Kalk WW, Bootsma, et al. Ann Rheum Dis 2007;66:107-12).

Combined gustatory and masticatory stimulatory techniques, such as those that employ lozenges, mints, and candies, are easy to implement, generally harmless (assuming that they are sugar free) and easy to use by most patients. If an acid is added, malic acid is preferred because this has less a harmful effect on tooth substance and oral mucosa. Frequent sips of water during the day can be the easiest and most efficacious technique to improve symptoms of dry mouth in some patients. Many patients like such an approach, even though water is a bad moistener of the oral mucosa: it wets the mucosa when exposed, but the mucosa gets quickly dry again as water does not 'stick' to the mucosa.

Figure 6. Some mucosal signs of oral dryness. (A) cracked, peeling and atrophic appearance of the lips, (B) dry and fissured tongue, (C) dry and smooth tongue. Note the signs of angular cheilitis, a common occurrence in dry mouth patients. ((A) courtesy Leo Sreebny).

Systemic salivary stimulation

The secretagogues pilocarpine and cevimeline are both muscarinic agonists that, in patients who have residual functional salivary gland tissue, induce a transient increase in salivary output and decrease the feeling of oral dryness.[26-29] Pilocarpine is a nonselective muscarinic agonist, whereas cevimeline reportedly has a higher affinity for M1 and M3 muscarinic receptor subtypes. Since M2 and M4 receptors are located on cardiac and lung tissues, cevimeline's M1 and M3 specificity suggest there will be fewer cardiac and/or pulmonary side effects.[43]

Common side effects of both medications include sweating, flushing, urinary urgency, and gastrointestinal discomfort. These side effects are frequent, but are rarely severe or serious. Parasympathomimetics are contraindicated in patients with uncontrolled asthma, narrow-angle glaucoma, or acute iritis and should be used with caution in pa-

Figure 7. Hyposalivation-related dental caries. Note the cervical lesions. These lesions occur in an area that in healthy subjects in cleansed by the continuous flow of saliva, whereas accumulation of dental plaque and food debris occurs in patients with reduced salivary flow.

tients with significant cardiovascular disease, Parkinson's disease, asthma, or chronic obstructive pulmonary disease. The best-tolerated doses for pilocarpine are 5 to 7.5 mg, given 3 or 4 times daily.[26,27] The duration of action is approximately 2 to 3 hours. Cevimeline is currently recommended at a dosage of 30 mg 3 times daily;[20,28] the duration of secretogogue activity is longer than pilocarpine (3 to 4 hours), whereas the onset is somewhat slower. In contrast to the United States, Canada, and Japan, cevimeline is not yet licensed in Europe.

Interferon-α has been tried via the oromucosal route. Initial studies looked promising, but later studies were less convincing. Furthermore, flu-like side effects and high costs make this way of treatment less attractive.[44]

Symptomatic treatment

In patients who do not respond to the various stimulation techniques cited earlier, several symptomatic treatments are available. Water, although less effective than the patients' natural saliva, is by far the most important fluid supplement for individuals with dry mouth. Patients should be encouraged to sip water and swish it around their mouth throughout the day. This will help to moisten the oral cavity, hydrate the mucosa, and clear debris from the mouth. Careful water drinking *with meals* is very important, since it will enhance taste perception, ease the formation of a bolus and improve mastication and swallowing (particularly for hard and fibrous foods). It will also help prevent choking and possible pulmonary aspiration. Patients should be counselled, however, that aqueous solutions do not produce long-lasting relief from oral dryness. Water wets the mucosa, but its moisture is not retained, since the mucous membranes of xerostomic patients are inadequately coated by a protective glycoprotein layer.[45]

Table 4. Management strategies for oral manifestations of Sjögren's syndrome.

Strategy	Approach	Description
Preventive measures	Regular dental visits and radiographs	• Usually every 3 to 4 months • Intraoral photographs every 6-18 months in dentate subjects who frequently develop new and recurrent caries lesions
	Optimal oral hygiene	• Guidance of team of oral health professionals (clinical instructions, written instructions)
	Topical fluorides and remineralising solutions	• Fluoride mouth rinse (0.1%,weekly) • Neutral sodium fluoride gel (depending on the level of oral hygiene and residual level of salivary flow: from once a week to every second day; the gel is preferably applied with a custom made tray)
	Diet modifications	• Noncariogenic diet • Minimise chronic use of alcohol and caffeine • Use of nonfermentable dietary sweeteners (xylitol, sorbitol, aspartame or saccharine), whenever possible
	Avoidance of drugs that may worsen sicca symptoms	• Caution when using antidepressants, antihistamines, anticholinergics, antihypertensives, neuroleptics
	Treatment of other medical conditions that result in xerostomia	• For example, endocrine disorders, metabolic diseases, viral infections
	Avoidance exacerbating factors	• Low humidity atmospheres such as air-conditioned stores, centrally heated houses, airplanes, windy locations • Avoiding irritants such as dust and cigarette smoke
Local salivary stimulation	Masticatory stimulatory techniques	• Sugar-free gums and mints
	Combined gustatory and masticatory stimulatory techniques	• Lozengers, mints, candies • Water, with or without a slice of lemon
Systemic salivary stimulation	Parasympathomimetic secretogogues	• Pilocarpine (5-7.5 mg, 3 to 4 times day) • Cevimeline (30 mg, 3 times/day)

Symptomatic treatment	Relief of oral dryness (nonresponders on systemic salivary stimulation)	• Use of air moisturisers • Frequent sips of water • Use of oral rinses, gels, and mouthwashes • Use of saliva substitutes • Increased humidification
	Oral candidiasis	• Topical antifungal drugs: - Nystatin oral suspension (100,000 U/mL: 400,000-600,000 units 4-5 times/day) - Clotrimazole cream (1%,2 times/day) - Ketoconazole cream (2%, 1-2 times/day) - Amphotericin B lozenge (10 mg, 4 times/day) • Systemic antifungal drugs: - Fluconazole tablets (200 mg on day 1, then 100mg/day for 7-14 days) - Itraconazole tablets (200 mg/day for 1-2 weeks) - Ketoconazole (200-400 mg/day for 7-14 days) • Dentures should be soaked in chlorhexine (2%) at night
	Angular cheilitis	• Nystatin cream or ointment (100,000 U/g, 4 to 5 times/day) • Clotrimazole cream (1%, 2 times/day) • Miconazole cream (2%, 1 to 2 times/day)
Treating underlying disorder	Systemic anti-inflammatory or immune modulating therapies to treat the autoimmune exocrinopathy of Sjögren's syndrome	• Rituximab

There are numerous oral rinses, mouthwashes and gels available for patients with dry mouth.[40,46-49] Patients should be cautioned to avoid products containing alcohol, sugar, or strong flavourings that may irritate the sensitive, dry oral mucosa. Saliva replacements (saliva substitutes or artificial salivas) are not well accepted over the long-term by many patients, particularly when not instructed properly.[46] As a guide to choosing the best substitute for a patient, the following recommendations for the treatment of hyposalivation can be used[47]:

- *Slight hyposalivation:* gustatory or pharmacological stimulation of the residual secretion is the treatment of choice. Little amelioration is to be expected from the use of saliva substitutes.
- *Moderate hyposalivation:* if gustatory or pharmacological stimulation of the residual salivary secretion does not ameliorate the dry mouth feeling, saliva substitutes with

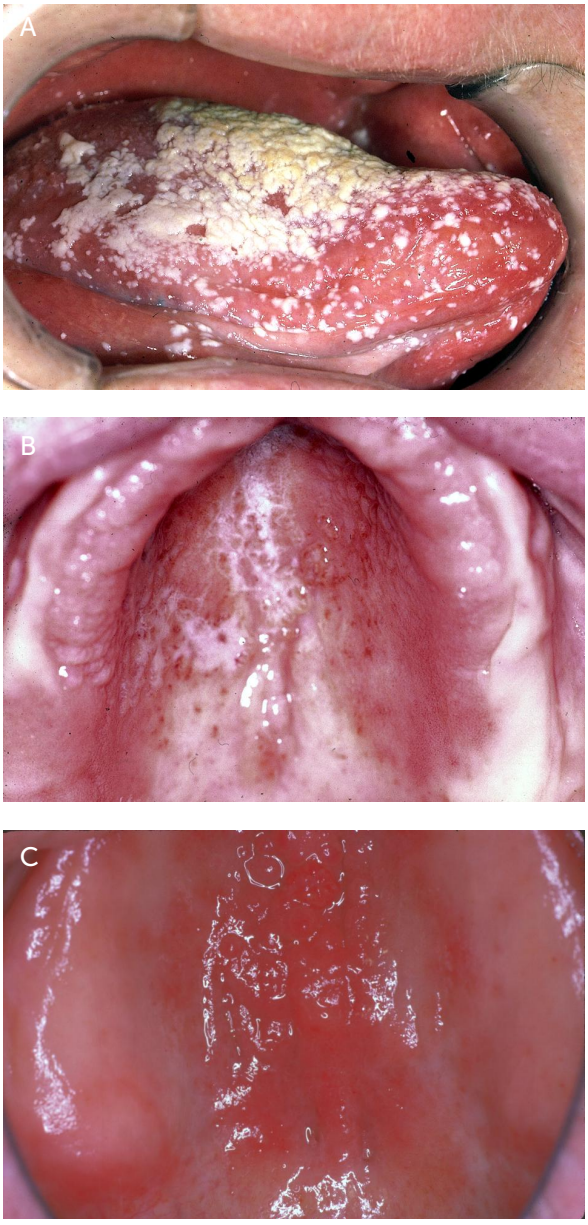

Figure 8. Candidiasis is a frequent sign in xerostomic patients. (A) white, curd-like mucocutaneous lesions, (B) atrophic candidiasis of the palate, (C) erythematous candidiasis of the palate.

Figure 9. Patient with Sjögren's syndrome who has developed a mucosa-associated lymphoid tissue (MALT) lymphoma in the left parotid gland.

a rather low viscoelasticity, such as substitutes which have carboxymethylcellulose, hydroxypropylmethylcellulose, mucin (porcine gastric mucin), or low concentrations of xanthan gum as a base are indicated. During the night or other periods of severe oral dryness, the application of a gel is helpful.

- *Severe hyposalivation:* a saliva substitute with gel-like properties should be used during the night and when daily activities are at a low level. During the day, a saliva substitute with properties resembling the viscoelasticity of natural saliva, such as substitutes which have xanthan gum and mucin (particularly bovine submandibular mucin) as a base, should be applied.[48,49]

Saliva is critical for the retention and comfort in wearing removable prostheses.[19] Lack of saliva at the denture-mucosal interface can produce denture sores due to a lack of lubrication and prosthesis retention. Hyposalivation is also associated with a decrease in the concentration of immune factors conferred on the oral mucosa by the salivary film that usually coats its surface. Insufficient denture stability and retention can cause social embarrassment, because prostheses dislodge during ordinary usage and can impair a person's ability or willingness to speak or eat, particularly in public.[50] Patients with inadequate saliva should moisten their dentures before they place them in their mouths.[51] Salivary substitutes, artificial saliva, salivary stimulants or just plain water can be used. All of these agents help with the adhesion, cohesion and retention of the denture. Patients can be advised to spray their prosthesis with artificial saliva prior to insertion of their dentures and before meals.

Prevention and treatment of oral candidiasis

Secondary infection of the mucosa with *Candida albicans* is not uncommon in patients with SS. Therefore, a high index of suspicion for fungal disease should be maintained, and appropriate antifungal therapies should be instituted as necessary (table 4). Patients with salivary gland dysfunction may require prolonged treatment to eradicate oral fungal infections.[52]

In denture wearing individuals, to prevent candidiasis, patient should not wear dentures over night, and the dentures should be soaked in an aqueous solution of 0.2% chlorhexine to prevent reinfections of the oral cavity by Candida species living in the denture material. Nystatin or clotrimazole cream can be used to treat angular cheilitis.

Systemic treatment for glandular manifestations

As mentioned for the treatment of ocular manifestations of SS, promising results have been reported with biological DMARDs. Relief of ocular and oral symptoms, fatigue, and other extraglandular manifestations was seen after treatment with anti-CD20 (rituximab), assessed with both subjective as well as objective measures.[30-35] These medications are discussed more extensively in the biologics section.

Management of dry surfaces other than mouth and eyes

Sicca symptoms elsewhere are treated symptomatically. Dry lips can be treated with lip salves or petroleum jelly, whereas dryness of the skin may require the use of moisturizing lotions and bath additives. Vaginal dryness can be relieved with lubricant jellies.

The use of humidifiers may also be helpful for nasal and pharyngeal dryness. Saline nasal sprays are available to resolve blocked nasal passages, which may occur as a result of nasal dryness. These sprays should be used frequently, since nasal blockage increases mouth breathing and exacerbate oral dryness. Additional causes of nasal blockage, such as nasal polyps and sinus infection, should be excluded and treated appropriately.

MANAGEMENT OF EXTRAGLANDULAR DISEASE

Most of the traditional anti-rheumatic drugs used in RA and SLE have been tried in pSS with limited results, especially for the glandular manifestations. These drugs, however, may be of benefit in the management of extraglandular manifestations. Biological DMARDs such as tumor necrosis factor (TNF) inhibitors, interferon-α (IFN-α) and B-cell depletion therapy have been tried in pSS with varying results, and research of their use is ongoing. The current treatment options available for extraglandular manifestations are summarised in table 5.

Anti-inflammatory and disease–modifying drugs

Fatigue, arthralgia, myalgia and low-grade fever are common nonexocrine manifestations of pSS.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line therapy of musculoskeletal and constitutional symptoms in pSS. However, pSS patients may have low tolerance of NSAIDs, resulting from dysphagia secondary to decreased salivary flow and esophageal dysmotility.

Corticosteroids are used in the treatment of arthritis, cutaneous symptoms, and severe constitutional manifestations of pSS. Low-dose prednisone up to 10 mg/day may relieve joint symptoms, pruritis, and mild leukocytoclastic vasculitis. A moderate dose of oral steroids up to 30 mg/day can be used in more severe cases of necrotic or ulcerating vasculitis. High-dose corticosteroids (1mg/kg/day) are used mainly in combination with immunosuppressants (mostly cyclophosphamide) to treat severe manifestations of SS, for example, in case of central nervous system or kidney involvement. In a controlled trial, corticosteroids had no significant effect on salivary and lacrymal function.[53] Whether pSS patients should be treated over a long period with corticosteroids is debatable, because pSS patients are more prone to acceleration of parodontitis and development of candidiasis (oral, vaginal) besides the other well-known side effects of corticosteroids use.

Hydroxychloroquine (200 to 400 mg daily) has been reported to improve features of immunologic hyperreactivity in patients with SS; however, a demonstrated clinical benefit is lacking. Hydroxychloroquine is mostly used for the treatment of cutaneous, musculoskeletal, and constitutional symptoms. In some cases, it can be of benefit for lupus-like skin manifestations in pSS.[54] In all conducted clinical trails, a decrease of serological parameters (IgG, ESR, ANA, RF, and interleukin-6 (IL-6)) was seen. The long-term effect of this drug needs to be assessed further.[55]

Methotrexate is used for polyarticular inflammatory arthritis in pSS, even though data on efficacy regarding arthritis in association with pSS are lacking. Benefit on sicca symptoms but no improvement on objective parameters was reported in a small study. Furthermore, no effect on serological parameters was found. A persistent elevation of hepatic transaminases was found more often in pSS compared with patients with RA and Wegener's granulomatosis.[56]

Azathioprine showed no effect on symptoms, signs, serology, histology, or disease activity in a controlled study. Even in low doses, a high frequency of adverse effects was seen. Azathioprine seems to have no place in the treatment of pSS.[57]

Sulphalazine has also failed to be effective in patients with pSS. It can result in various severe side effects such as meningitis and hepatitis, and it may also induce ulcerative colitis or SLE in pSS patients.[58]

Leflunomide was recently studied in a small open-label study. A modest but not significant improvement of salivary and lacrimal gland function was seen. The drug showed

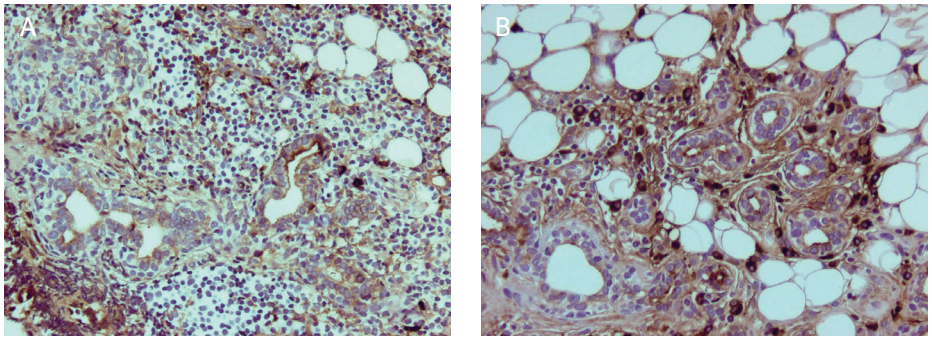

Figure 10. Biopsy from the parotid gland taken before starting rituximab and 12 weeks after rituximab treatment. Staining for immunoglobulin A (IgA). (A) before treatment a dense infiltrate and disordered ductal structures with a paucity of IgA plasma cells is present. (B) after rituximab the infiltrate has almost disappeared with a more regular structure of ducts and a predominance of IgA plasma cells.

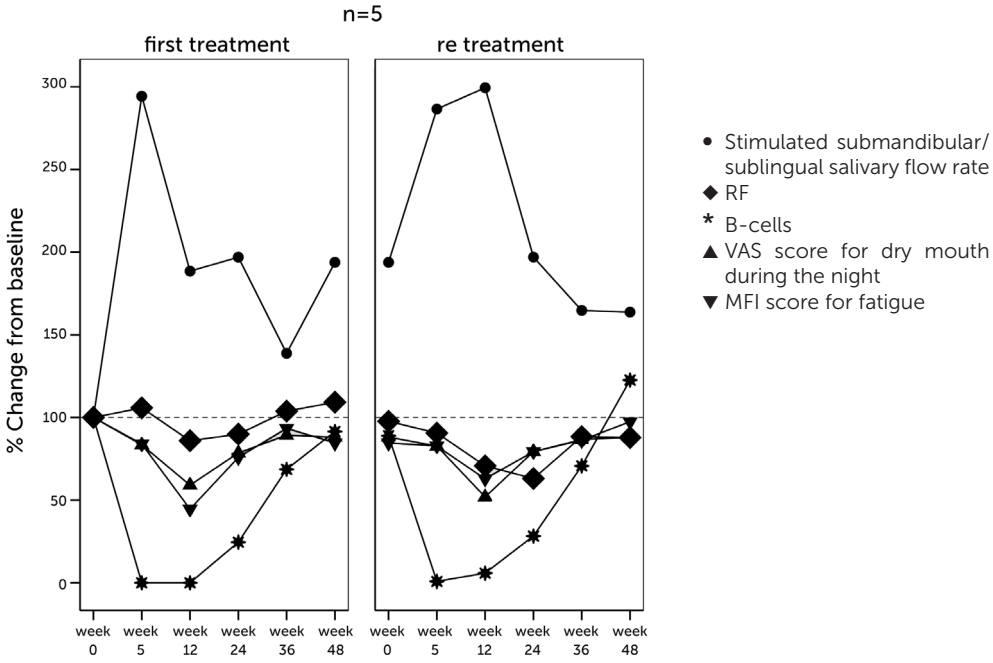

Figure 11. Increase and decrease (mean values of 5 pSS patients) in stimulated submandibular/sublingual flow rate, RF, B-cells, VAS score for dry mouth during the night and MFI score for fatigue following rituximab (re)treatment (baseline is 100%). Baseline values (week 0 first treatment) were stimulated submandibular/sublingual flow rate 0.09±0.07 ml/minute, RF 339±329 kIU/L, B-cells 0.19±0.09 10^9/L, VAS score for dry mouth during the night 85±12, MFI score for fatigue 16±3. (From Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren's syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5).

Figure 12. Purpura as an extraglandular manifestation.

an acceptable safety profile in most patients; however, in several cases, an exacerbation of leucocytoclastic vasculitis was seen. A controlled study is needed to decide the place of this drug.[59]
Mycophenolate Mofetil (MMF) has not yet been tested in pSS patients.

Other systemic drugs

Dehydroepiandrosterone sulphate (DHEA) was tried in women with pSS because of the female predominance in pSS, the demonstration of decreased serum levels of conjugated dihydrotestosterone in female pSS patients, and the finding that HR-QoL in pSS correlates with circulating levels of DHEA-sulfate. However, in a controlled trial, no evidence for efficacy of DHEA was found, except for subjective improvement of dry mouth.[60]

Biological DMARDs

At present, biological DMARDs have been introduced in the treatment of various systemic autoimmune diseases, for example, RA and SLE. The biological DMARDs most frequently used in the treatment of autoimmune diseases are monoclonal antibodies, soluble receptors, and molecular imitators.[61] These biological DMARDs enhance or replace conventional immunosuppressive therapy. In contrast to RA and SLE, no biological DMARDs has yet been approved for the treatment of SS, but several phase II and III studies have been conducted or are currently being conducted. The biological DMARDs used in SS trials are IFN-α and agents targeting TNF and B-cells (anti-CD20, anti-CD22).

Although no trials have yet been performed with B-cell activating factor (BAFF) antagonists, these antagonist are thought to be a promising therapy[62] and are also discussed in this chapter.

Interferon-α

IFNs are proteins with antiviral activity and potent immunomodulating properties. SS patients have an activated type I IFN system.[63] In a phase II study, treatment of pSS patients with IFN-α administered via the oromucosal route (by dissolving lozenges) demonstrated some efficacy and appeared safe.[64] Based on these promising results, a randomised, parallel group, double-blinded, placebo-controlled clinical trial (497 pSS patients) was designed. Patients were randomised into 2 groups and received 24 weeks of daily treatment with either 450 IU IFN-α (150 IU 3 times per day) or a placebo lozenge in a ratio 3:2, administered by the oromucosal route. This randomised controlled clinical trial failed to demonstrate a significant effect on the primary endpoints (Visual Analogue Scale (VAS) score for oral dryness and stimulated whole salivary flow rate) in the IFN-α group relative to the placebo group. However, there was a significant increase in unstimulated whole salivary flow rate in the patients treated with IFN-α, which correlated positively and significantly with improvement in 7 of 8 symptoms associated with oral and ocular dryness. No adverse events were observed.[44]

In conclusion, no clinical evidence for the efficacy of IFN-α treatment in pSS patients has been shown, although an increase in the unstimulated whole salivary flow rate was observed. Further research is needed to clarify the effects of IFN-α on salivary gland tissue.

Anti-tumor necrosis factor

There are currently 3 biological DMARDs targeting TNF: the chimeric monoclonal antibody infliximab, the receptor fusion protein etanercept, and the fully humanised monoclonal antibody adalimumab.

In an open-label study, treatment with infliximab was reported to be effective in active pSS over a 3-month period.[65] In a follow-up study, retreatment of the patients induced an improvement of SS-related signs that was comparable with the effects from the first 3 infusions.[66] To confirm these promising results from an uncontrolled study, the Trial of Remicade In Primary Sjögren's Syndrome (TRIPPS) study was designed. In this double-blinded, placebo-controlled randomised clinical trial, 103 patients with active pSS were included and treated with infliximab (5 mg/kg) or placebo infusions at weeks 0, 2 and 6. The follow-up time was 22 weeks, and the primary endpoint was an improvement by greater than 30% in 2 of 3 VAS scores (joint pain, fatigue, and dry eyes). In contrast to the previously mentioned uncontrolled studies, no evidence of efficacy of infliximab treatment on clinical or functional parameters could be demonstrated in this trial.[67] These disappointing results also underscore the difficulty of interpreting uncontrolled data in chronic autoimmune diseases.

In a pilot trial of etanercept, 25 mg subcutaneously twice a week for 12 weeks in 15 pSS patients (mean disease duration 3.6 years), no reduction of sicca symptoms or signs were seen, nor did continued treatment for up to 26 weeks show beneficial effects in the total group of patients.[68] Another trial evaluating etanercept versus placebo for 12 weeks in 28 patients also failed to show clinical efficacy.[69]
No trials of adalimumab treatment in pSS have been reported in the literature.
In conclusion, TNF-targeting treatment could not be proven to be of benefit in reducing the signs and symptoms of pSS.

Anti-CD20 monoclonal antibodies
Anti-CD20 (e.g., rituximab) is a chimeric monoclonal antibody specific for the B-cell surface molecule CD20. CD20 is expressed on the surface of normal and malignant pre-B and mature B lymphocytes. Rituximab has been demonstrated to induce lysis of B-cells by complement-dependent and antibody-dependent cytotoxicity mechanisms, as well as by direct induction of apoptosis.[70]
Rituximab is currently used for the treatment of low-grade B-cell lymphomas.[71] In controlled studies, it was shown to be safe and effective in the treatment of RA.[72-74] Moreover, some promising open-label studies in SLE patients have been published.[75]
Two studies retrospectively evaluated the effect of rituximab (4 infusions of 375 mg/m^2) in 18 pSS patients (mean disease duration 10 years) with systemic features. Self-reported dryness improved in 6 patients (VAS scores not known for 3 patients, no improvement in the other 9 patients). Both studies reported good efficacy of the treatment on systemic features.[30,32]
In an open-label phase II study, 15 patients with pSS were treated with 4 infusions of rituximab (375 mg/m^2 once weekly) and followed for a 3-month period. Eight of the 15 patients were early pSS patients (mean disease duration 28 months, all had residual salivary gland function at baseline) and 7 patients had a concomitant MALT lymphoma (mean disease duration 79 months). In the early pSS patients, rituximab treatment resulted in significant improvement of subjective symptoms and an increase in salivary gland function. All patients showed a rapid depletion of peripheral B-cells within a few weeks, accompanied by a decrease in RF levels.[31] Repeated parotid gland biopsies in 5 of the early patients after treatment, showed redifferentation of the lymphoepithelial duct lesions into normal striated ducts, possibly indicating regeneration of salivary gland tissue (figure 10).[76]
Five of the 8 pSS patients without a MALT-lymphoma received a second course of rituximab (after 9-11 months) due to recurrence of symptoms. Retreatment resulted in the same significant improvement of the salivary flow rate and subjective symptoms compared with the results of the first treatment, together with a decrease in B-cells and RF levels (figure 11).[77]
Six of the 7 MALT/pSS patients were initially effectively treated with rituximab. The re-

Table 5. Management strategies for extraglandular manifestations of Sjögren's syndrome.

Symptom		Treatment
Severe fatigue		• NSAIDs • Hydroxychloroquine (400 mg/day) • Prednisone (7.5-10 mg/day; max 15 mg)
Anorexia		• Hydroxychloroquine (400 mg/day) • Prednisone (7.5-10 mg/day; max 15 mg)
Arthralgia		• NSAIDs
Myalgia		• NSAIDs
Arthritis		• NSAIDs • Hydroxychloroquine (400 mg/day) • Methotrexate (15 mg/week; max 25 mg) • Prednisone (7.5-10 mg/day; max 15 mg)
Skin involvement	Mild vasculitis	• Hydroxychloroquine (400 mg/day) and/or prednisone (7.5-10 mg/day; max 15 mg)
	Polymorphic erythema	• Hydroxychloroquine (400 mg/day; max 800mg) and or prednisone (7.5-10 mg/day; max 15 mg)
	Raynaud	• Calcium channel blocker
Severe vasculitis		• Prednisone (60 mg/day) with or without cyclophosphamide IV (750 mg/m2/month; 6-12 times)
Pulmonary involvement	Pleuritis / serositis	• NSAIDs • Prednisone (15-20 mg/day; max 30 mg)
	Interstitial pneumonitis	• Prednisone (60 mg/day) with or without cyclophosphamide IV (750 mg/m2/month; 6-12 times)
Esophageal dysfunction		• Omeprazol (20-40 mg/day)

Neurological involvement	Severe PNS	• Prednisone (60 mg/day) with or without cyclophosphamide IV (750 mg/m2/month; 6-12 times)
	CNS	• Prednisone (60 mg/day) with or without cyclophosphamide IV (750 mg/m2/month; 6-12 times)
Interstitial cystitis		• Pilocarpine (5-7.5 mg, 3 times/day) and/or prednisone (15 mg/day)
Renal involvement	Interstitial nephritis	• Bicarbonate (individual dose) and/or potassium completion (individual dose) • Prednisone (15-60 mg/day, depending on severity of proteinuria or renal impairment)
	Glomerulonephritis	• Prednisone (60 mg/day) with or without cyclophosphamide IV (750 mg/m2/month; 6-12 times)
MALT lymphoma	With no active SS	• Careful watching
	With symptomatic enlarged parotid gland(s), no active SS	• Radiotherapy (2x2 Gy)
	With active SS	• Rituximab IV (375 mg/m^2; weekly; 4 times), cyclophosphamide IV (750 mg/ m^2; 3-weekly; 8 times), and prednisone (100 mg during 5 following days after cyclophosphamide infusions; 8 times)

maining MALT/pSS patient had progressive MALT disease and severe extraglandular SS disease within 3 months after the start of rituximab treatment. Cyclophosphamide was added, which led to stable disease of both MALT and SS. One of the 6 patients initially responding had a recurrence of MALT lymphoma after 9 months and was successfully retreated with rituximab. The other patients are still in remission (unpublished data).
In another open-label study, 16 pSS patients received only 2 weekly rituximab infusions (375mg/m^2), with a follow-up of 36 weeks. Again, treatment resulted in rapid complete depletion of peripheral B-cells. At week 12, a significant improvement of VAS scores for fatigue and dryness was recorded, and at week 36, a significant improvement for VAS scores for global disease, fatigue, dry mouth, dry eyes, and dry vagina, but also in the number of tender joint and tender point was reported.[33] Both in the study by Pijpe and

associates[31] and the study by Devauchelle-Pensec and coworkers,[33] patients with a short disease duration showed more improvement than patients with longer disease duration. Two double-blind randomised placebo-controlled trials have been performed. One trial focused on fatigue as the primary outcome parameter. In this trail with a total of 17 patients with pSS and a follow-up of 6 months, a significant improvement was seen from baseline on fatigue by VAS in the rituximab group in contrast to the placebo group. In addition, social functioning assessed with the short-form 36 (SF-36) was also significantly different between the groups at 6 months.[34] The other trial focused on salivary gland function as the primary endpoint. In this trial with 30 patients and a follow-up of 12 months, salivary secretion improved in the rituximab group and decreased in the placebo group. The VAS score for oral dryness improved in the rituximab group and slightly deteriorated in the placebo group. The Multidimensional Fatigue Index (MFI) score for general fatigue improved in both groups; the largest improvement was observed in the rituximab-treated patients, with disease duration less than 4 years. The number of extraglandular manifestations decreased in the rituximab group, whereas the number of extraglandular manifestations increased in the placebo group. B-cells were completely depleted in all patients treated with rituximab after the first infusion. RF level (kIU/L) decreased in the rituximab group and slightly increased in the placebo group.[35]

In conclusion, in phase II trials, it has been shown that rituximab seems to be effective for at least 6 to 9 months in patients with active pSS, improving both subjective symptoms and objective signs of the disease. Retreatment with rituximab resulted in a similar good clinical response. In pSS patients with longer disease duration and lacking residual salivary gland function, rituximab treatment seemed to be effective for systemic features, but no recovery of salivary flow was observed. To confirm these promising results, randomised placebo-controlled clinical trials are needed.

Anti-CD22 monoclonal antibodies

Epratuzumab is a humanised monoclonal antibody specific for the B-cell surface molecule CD22, which is expressed on the surface of normal mature and malignant B lymphocytes. CD22 appears to be involved in the regulation of B-cell activation through B-cell receptor signaling and cell adhesion.[78] In an open-label phase I and II study, safety and efficacy of epratuzumab was investigated in 16 pSS patients. Follow-up was 6 months. These pSS patients received 4 doses of 360 mg/m^2 epratuzumab intravenously. In contrast to rituximab, no complete depletion of peripheral B-cells was induced, but a median decrease of 54% and 39% at 6 and 18 weeks, respectively. Improvements occurred in the Schirmer's test, the level of unstimulated whole salivary flow rate, and the VAS score for fatigue. Remarkably, the number of responders was higher at 6 months after the treatment administration than at earlier time points. Epratuzumab seems to be a promising treatment, and randomised, placebo-controlled clinical trials are needed.[79]

Anti-BAFF

BAFF is a B-cell activating factor that acts as a positive regulator of B-cell function and expansion. BAFF levels were found elevated in serum and saliva in SS patients, but no correlation was observed between serum and saliva levels.[80] However, circulating levels of BAFF in pSS patients were shown to be a marker for disease activity.[81]

At present, 2 human BAFF antagonists have been developed: belimumab, a human antibody (anti-BLyS) that binds to soluble BAFF; and atacicept, a fusion protein of 1 of the BAFF receptors.[82,83] Especially SS patients with elevated BAFF levels, hypergammaglobulinemia, elevated levels of autoantibodies, and associated B-cell lymphoma might be candidates for anti-BAFF treatment.[84] Levels of BAFF increase after B-cell depletion therapy, which could favor the re-emergence of auto-reactive B-cells. Therefore, BAFF antagonist treatment in combination with rituximab could be considered to prolong the period of remission after rituximab infusion.[85] Until now, no trials with anti-BAFF treatment in SS have been published.

Safety and tolerability of biological DMARDs

The most important immediate side effects of treatment with biological DMARDs are infusion reactions. Most of these side effects are mild, but in SS, a more serious serum sickness-like disease has occurred with rituximab. This adverse effect of treatment occurred in 16% (8 of 49) of the patients treated with rituximab in the open-label study of Pijpe and colleagues,[31] and it may be related to the formation of antibodies against the biological DMARDs (human antichimeric antibodies (HACA's), because HACA formation was indeed observed in these patients. Serum sickness-like disease occurred only in patients receiving low-dose corticosteroids and no other immunosuppressive drugs, whereas higher doses of corticosteroids during treatment might prevent the occurrence of this complication. Indeed in the randomised placebo-controlled clinical trial of Meijer and associates,[35] which included higher doses of corticosteroids, the incidence serum sickness was strongly reduced.

Some patients developed infections following treatment with treatment with biological DMARDs, but some of these patients also used other immunosuppressive therapies.

Treatment strategies in severe extraglandular manifestations

The extraglandular manifestations of SS can be divided in 2 different categories; the periepithelial and the extraepithelial involvement, having different prognostic significance. Patients with periepithelial lesions, such as liver and lung involvement, interstitial cystitis, or interstitial nephritis (renal tubular acidosis), usually have more stable disease. If needed, these manifestations can be treated with a low or intermediate dose of prednisone. Patients suffering predominantly of extraepithelial manifestations of the disease have a higher morbidity and mortality. Examples of these manifestations are glomerulonephritis (mesangial or membranoproliferative), polyneuropathy, purpura (figure 12),

and vasculitis. The more severe manifestations are associated with the following serological parameters: lymphopenia, cryoglobulinemia, and low complement levels (C4).[86] These extraglandular manifestations, in combination with the serological parameters and persistently swollen parotid glands, are predictors of MALT lymphoma. Close monitoring and sometimes aggressive treatment are needed in these patients. Treatment consists mostly of a combination of high-dose corticosteroids with cyclophosphamide, with or without B-cell depletion therapy.

Nephritis

Two types of kidney involvement are seen in pSS, namely interstitial nephritis and glomerulonephritis. Interstitial nephritis is seen in 30% of patients and leads to clinical symptoms in 5 to 10% of patients. A distal or proximal renal tubular acidosis (RTA I or II) can result in clinical symptoms such as compromised renal function, proteinuria, nephrocalcinosis, kidney stones, hypokalemia, hypophosphatemia, polyuria, and nephrogenic diabetes insipidus. In mild cases, only supplementation with bicarbonate and potassium is recommended. In more severe cases, intermediate or high doses of prednisone are added. In 5 to 10% of the patients, an immune complex-mediated mesangial or membranoproliferative nephritis is seen, leading to clinical findings such as hypertension, proteinuria (mild to nephritic syndrome) and to active urinary sediment with erythrocytes and casts. These patients are treated with a combination of high-dose prednisone (1mg/kg/day) and cyclophosphamide (750/m^2/month; 6-12 times). In case of glomerulonephritis in combination with a MALT lymphoma, adding rituximab (375mg/ m^2/week; 4 times), is recommended.

Neurological manifestations

Central nervous manifestations associated with pSS are either focal or diffuse. They are treated with high doses of corticosteroids. In case of diffuse symptoms based on vasculitis, pulse cyclophosphamide is added to the high doses of prednisone. In an acute setting or when symptoms are worsening, treatment with plasmapheresis and or intravenous immunoglobulins (IVIG) may be considered.[87]

Involvement of the peripheral nervous system affects about 10 to 20% of the patients with pSS, mainly in the form of sensorimotor and sensory polyneuropathies and cranial neuropathies. These manifestations respond poorly to corticosteroids, but stabilisation or spontaneous improvements were seen. Axonal neuropathy also responds badly to corticosteroids. Successful treatment with plasmapheresis and/or IVIG was described in anecdotal reports. On the contrary, in mononeuritis multiplex with nerve biopsies revealing vasculitis treatment with high doses of corticosteroids and pulse cyclophosphamide was found to be useful.

For neurological manifestations, no studies of early treatment are available. The role of rituximab for the treatment of neurological manifestations should be explored further.[88]

Vasculitis

Skin lesions based on vasculitis are seen in 10% of pSS patients. Mostly common are purpura, polymorphic erythema, urticarial lesions, and ulcers based on a leukocytoclastic vasculitis. Systemic vasculitis can lead to neuropathic, renal, pulmonary, and gastrointestinal symptoms. These manifestations are associated with cryoglobulinemia and low complement levels. Corticosteroids are the first step in treatment. In more severe cases, a combination of corticosteroids and intravenous cyclophosphamide is given. In life-threatening situations, treatment is started with plasmapheresis or IVIG, followed by intravenous corticosteroids and cyclophophamide. Rituximab, especially in patients with cryoglobulinemia, may be successful; however, this has yet to be proved in controlled trials.[89]

Haematologic complications

Most haematologic complications are asymptomatic and include mild autoimmune cytopenias and hyperglobulinemia. No specific therapy is necessary, but these patients need careful follow-up. For more severe cytopenias aggressive treatment is indicated. Autoimmune haemolytic anemia, thrombocytopenia, and agranulocytosis are treated with corticosteroids. If response is not sufficient, cyclophosphamide is added. Treatment with azathioprine is not recommended because it may facilitate the development of lymphoproliferative disorders in pSS patients who already are at increased risk for development of B-cell lymphomas. Plasmapheresis, IVIG and rituximab are second- or third-line options in severe haemolytic anemia and thrombocytopenic purpura.

Mucosa-associated lymphoid tissue lymphoma

The therapeutic approach to SS patients with MALT lymphoma is still a matter of debate. Based on our experience[31] and that of others[90] the following approach seems justified. In patients with asymptomatic MALT lymphoma restricted to the salivary glands, a "wait and see" policy can be chosen. These localized MALT lymphomas, which are frequently diagnosed coincidentally by pathologists when evaluating parotid gland biopsies, show a benign course with a good prognosis. For a symptomatic localized MALT lymphoma, local radiotherapy, or 8 cycles of R-CP (intermittent courses of IV rituximab, 375 mg/m^2; IV cyclophosphamide, 750 mg/m^2; and oral prednisone, 60 mg/m^2, for 5 days) are indicated. Disseminated MALT lymphoma should be treated with 8 cycles of R-CP. In case of high-grade lymphoma, which is seen far less frequently than MALT lymphoma, cyclophosphamide / doxorubicin / vincristine / prednisone in combination with rituximab (CHOP-R) is the therapy of choice.

FUTURE PERSPECTIVES

Because many SS patients suffer from reduced HR-QoL and are restricted in social and

work related activities, there is a great need for development of adequate treatment modalities to reduce SS-related complaints and to intervene in the progression of SS.
Biological DMARDs are promising therapies for SS, but not all biological DMARDs studied were found to be effective. Thus, on the one hand randomised studies failed to show a clinical effect of anti-TNF and IFN-α in the treatment of SS, whereas B-cell depletion (both with rituximab and epratuzumab) seems promising. Other potential targets for biological therapy include cytokines such as IL-6 and BAFF, adhesion molecules, and chemokines. In patients with active autoimmune disease monoclonal antibodies may be more immunogenic, because HACAs have occurred at a higher rate, and serum sickness-like disease was observed in pSS patients with active disease, but not in patients with pSS and MALT. Additional use of immunosuppressive therapy in SS patients with high disease activity might be mandatory to prevent serious side effects. These unwanted side effects might also be prevented by the use of fully humanised antibodies. The currently available humanised antibodies are promising but need further study.
Besides the availability of an effective treatment, there is still a need for improved assessment parameters to monitor treatment effects, both subjectively and objectively. For studies on intervention of SS, evaluation of the parotid gland might be of use because function, composition of saliva (repeated collections), and histology (repeated biopsies) can be evaluated on the same parotid gland at different time points. In addition, activity scores are currently being developed.[91-93] The development and widespread use of disease activity and disease damage indices may facilitate the evaluation of new treatment options in SS.

ACKNOWLEDGEMENTS

We would like to thank Cees GM Kallenberg, Nicole Kamminga, and Khaled Mansour for their contributions to this chapter.

References

1 Fox RI. Sjögren's syndrome. Lancet 2005;366:321-31.

2 Hansen A, Lipsky PE, Dorner T. Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. Curr Opin Rheumatol 2005;17:558-65.

3 Meijer JM, Meiners PM, Huddleston-Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology 2009;48:1077-82.

4 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-58.

5 Daniels TE. Labial salivary gland biopsy in Sjögren's syndrome. Assessment as a diagnostic criterion in 362 suspected cases. Arthritis Rheum 1984;27:147-56.

6 Pijpe J, Kalk WW, van der Wal JE, et al. Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46:335-41.

7 Pijpe J, Kalk WW, Bootsma H, et al. Progression of salivary gland dysfunction in patients with Sjögren's syndrome. Ann Rheum Dis 2007;66:107-12.

8 Suzuki S, Kawashima K. Sialographic study of diseases of the major salivary glands. Acta Radiol Diagn (Stockh) 1969;8:465-78.

9 Kalk WW, Vissink A, Spijkerbet FK, et al. Morbidity from parotid gland sialography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:572-75.

10 Blatt IM, French AJ, Holt JF, et al. Secretory sialography in diseases of the major salivary glands. Ann Otol Rhinol Laryngol 1956;65:295-317.

11 Blatt IM. On sialectasis and benign lymphosialdenopathy (the pyogenic parotitis, Gourgerot-Sjoegren's syndrome, Mikuliciz's disease complex). A ten-year study. Laryngoscope 196;74:1684-746.

12 Hermann GA, Vivino FB, Goin JE. Scintigraphic features of chronic sialadenitis and Sjögren's syndrome: a comparison. Nucl Med Commun 1999;20:1123-32.

13 Roescher N, Illei GG. Can quantified salivary gland scintigraphy results aid diagnosis of patients with sicca symptoms? Nat Clin Pract Rheumatol 2008;4:178-9.

14 Tzioufas AG, Mitsias DI, Moutsopoulos HM. Sjögren syndrome. In: Hochberg MC, Silman AJ, et al, editors. Rheumatology. Philadelphia: Elsevier; 2008. p.1348-9.

15 Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med 2004;164:1275-84.

16 Vissink A, Kalk WW, Mansour K, et al. Comparison of lacrimal and salivary gland involvement in Sjögren's syndrome. Arch Otolaryngol Head Neck Surg 2003;129:966-71.

17 Dormenval V, Budtz-Jorgensen E, Mojon P, et al. Assiociations between malnutrition, poor general health and oral dryness in hospitalised elderly patients. Age Ageing 1998;27:123-8.

18 Walls AW, Steele JG. The relationship between oral health and nutrition in older people. Mech Ageing Dev 2004;125:853-7.

19 Guggenheimer J, Moore PA. Xerostomia: etiology, recognition and treatment. J Am Dent Assoc 2003;134:61-9.

20 Fox PC, van der Ven PF, Sonies BC, et al. Xerostomia. Evaluation of a symptom with increasing significance. J Am Dent Assoc 1985;110:519-25.

21 Tanida T, Okamoto T, Okamoto A, et al. Decreased excretion of antimicrobial proteins and peptides in saliva of patients with oral candidiasis. J Oral Pathol Med 2003;32:586-94.

22 Skopouli FN, Dafni U, Ioannidis JP, et al. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000;29:296-304.

23 Tzioufas AG, Boumba DS, Skopouli FN, et al. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjögren's syndrome. Arthritis Rheum 1996;39:767-72.

24 Lemp MA. Management of dry eye disease. Am J Manag Care 2008;14:S88-101.

25 Mansour K, Leonhardt CJ, Kalk WW, et al. Lacrimal punctum occlusion in the treatment of severe keratoconjunctivitis sicca caused by Sjögren's syndrome: an uniocular evaluation. Cornea 2007;26:147-50.

26 Vivino FB, Al Hashimi I, Khan Z, et al. Pilocarpine tablets for the treatment of dry mouth and dry eye symptoms in patients with Sjögren syndrome: a randomised, placebo-controlled, fixed-dose, multicenter trial. P92-01 Study Group. Arch Intern Med 1999;159:174-81.

27 Papas AS, Sherrer YS, Charney M, et al. Successful treatment of dry mouth and dry eye symptoms in Sjögren's syndrome patients with oral pilocarpine: a randomised, placebo-controlled, dose-adjustment study. J Clin Rheumatol 2004;10:169-77.

28 Petrone D, Condemi JJ, Fife R, et al. A double-blind, randomised, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 2002;46:748-54.

29 Fife RS, Chase WF, Dore RK, et al. Cevimeline for the treatment of xerostomia in patients with Sjögren syndrome: a randomised trial. Arch Intern Med 2002;162:1293-300.

30 Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B-cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis 2007;66:351-7.

31 Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005;52:2740-50.

32 Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;64:913-20.

33 Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007;57:310-7.

34 Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren's syndrome with rituximab: results of a randomised, double-blind, placebo controlled pilot study. Ann Rheum Dis 2008;67:1541-4.

35 Meijer JM, Meiners PM, Vissink A, et al. Effective rituximab treatment in primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled trial. Arthritis Rheum 2010;960-8.

36 Chalmers JM. Minimal intervention dentistry: part 1. Strategies for addressing the new caries challenge in older patients. J Can Dent Assoc 2006;72:427-33.

37 Jansma J, Vissink A, Gravenmade EJ, et al. In vivo study on the prevention of postradiation caries. Caries Res 1989;23:172-8.

38 Anusavice KJ. Dental caries: risk assessment and treatment solutions for an elderly population. Compend Contin Educ Dent 2002;23(10Suppl.):12-20.

39 Kielbassa AM, Hinkelbein W, Hellwig E, et al. Radiation-related damage to dentition. Lancet Oncol 2006;7:326-35.

40 Zero DT. Dentifrices, mouthwashes, and remineralisation/caries arrestment strategies. BMC Oral Health 2006:6(Suppl.1):S9.

41 Walsh L. Lifestyle impacts on oral health. Preservation and resoration of tooth structure. Middlesbrough, UK:Knowledgebooks and Software Ltd.;2008.p.83-110.

42 Van Loveren C. Sugar alcohols: what is the evidence for caries-preventive and caries-therapeutic effects? Caries Res 2004;38:286-93.

43 Chambers MS, Jones CU, Biel MA, et al. Open-label, long-term safety study of cevimeline in the treatment of postirradiation xerostomia. Int J Radiat Oncol Biol Phys 2007;69:1369-76.

44 Cummins MJ, Papas A, Kammer GM, et al. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. Arthritis Rheum 2003;49:585-93.

45 Vissink A, de Jong HP, Busscher HJ, et al. Wetting properties of human saliva and saliva substitutes. J Dent Res 1986;65:1121-4.

46 Fox PC, Brennan M, Pillemer S, et al. Sjögren's syndrome: a model for dental care in the 21th century. J Am Dent Assoc 1998;129:719-28.

47 Regelink G, Visink A, Reintsema H, et al. Efficacy of a synthetic polymer saliva substitute in reducing oral compaints of patients suffering from irradiation-induced xerostomia. Quintessence Int 1998;29:383-8.

48 Epstein JB, Emerton S, Le ND, et al. A double-blind crossover trial of oral balance gel and biotene toothpaste versus placebo in patients with xerostomia following radiation therapy. Oral Oncol 1999;35:132-7.

49 Ship JA, McCutcheon JA, Spivakovsky S, et al. Safety and effectiveness of topical dry mouth products containing olive oil, betain, amd xylitol in reducing xerostomia for polypharmacy-induced dry mouth. J Oral Rehabil 2007;34:724-32.

50 Turner M, Jahangiri L, Ship JA. Hyposalivation, xerostomia and the complete denture: a systemic review. J Am Dent Assoc 2008;139:146-50.

51 Zarb G, Bolender C, Eckers S. Prothodontic treatment for edentulous patients. 12th ed. St. Louis: Mosby; 2008.

52 Daniels TE, Fox PC. Salivary and oral components of Sjögren's syndrome. Rheum Dis Clin North Am 1992;18:571-89.

53 Fox PC, Datiles M, Atkinson JC, et al. Prednisone and piroxicam for treatment of primary Sjögren's syndrome. Clin Exp Rheumatol 1993;11:149-56.

54 Dawson LJ, Caulfield VL, Stanbury JB, et al. Hydroxychloroquine therapy in patients with primary Sjögren's syndrome may improve salivary gland hypofunction by inhibition of glandular cholinesterase. Rheumatology (Oxford) 2005;44:449-55.

55 Kruize AA, Hene, Kallenberg CG, et al. Hydroxychloroquine treatment for primary Sjögren's syndrome: a two year double blind crossover trial. Ann Rheum Dis 1993;52:360-4.

56 Skopouli FN, Jagiello P, Tsifetaki N, et al. Methotrexate in primary Sjögren's syndrome. Clin Exp Rheumatol 1996;14:555-8.

57 Price EJ, Rigby SP, Clancy U, et al. A double blind placebo controlled trial of azathioprine in het treatment of primary Sjögren's syndrome. J Rheumatol 1998;25:896-9.

58 Thanou-Stavraki A, James JA. Primary Sjögren's syndrome: current and prospective therapies. Semin Arthritis Rheum 2008;37:273-92.

59 van Woerkom JM, Kruize AA, Geenen R, et al. Safety and efficacy of leflunomide in primary Sjögren's syndrome: a phase II pilot study. Ann Rheum Dis 2007;66:1026-32.

60 Hartkamp A, Geenen R, Godaert GL, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjögren's syndrome: a randomised controlled trial. Ann Rheum Dis 2008;67:91-7.

61 Kourbeti IS, Boumpas DT. Biological therapies of autoimmune diseases. Curr Drug Targets Inflamm Allergy 2005;4:41-6.

62 d'Arbonneau F, Pers JO, Devauchelle V, et al. BAFF-induced changes in B-cell antigen receptor-containing lipid rafts in Sjögren's syndrome. Arthritis Rheum 2006;54:115-26.

63 Bave U, Nordmark G, Lovgren T, et al. Activation of the type I interferon system in primary Sjögren's syndrome: a possible etiopathogenic mechanism. Arthritis Rheum 2005;52:1185-95.

64 Ship JA, Fox PC, Michalek JE, et al. Treatment of primary Sjögren's syndrome with low-dose natural human interferon-alpha administered by the oral mucosal route: a phase II clinical trial. IFN Protocol Study Group. J Interferon Cytokine Res 1999;19:943-51.

65 Steinfeld SD, Demols P, Salmon I, et al. Infliximab in patients with primary Sjögren's syndrome: a pilot study. Arthritis Rheum 2001;44:2371-5.

66 Steinfeld SD, Demols P, Appelboom T. Infliximab in primary Sjögren's syndrome: one-year follow-up. Arthritis Rheum 2002;46:3301-3.

67 Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of inflixmab in primary Sjögren's syndrome: results of the randomised controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). Arthritis Rheum 2004;50:1270-6.

68 Zandbelt MM, de Wilde P, van Damme P, et al. Etanercept in the treatment of patients with primary Sjögren's syndrome: a pilot study. J Rheumatol 2004;31:96-101.

69 Sankar V, Brennan MT, Ko MR, et al. Etanercept in Sjögren's syndrome: a twelve-week randomised, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240-5.

70 Salama AD, Pusey CD. Drug insight: ritixumab in renal disease and transplantation. Nat Clin Pract Nephrol 2006;2:221-30.

71 McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Ritiximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16:2825-33.

72 Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572-81.

73 Edwards JC, Cambridge G. B-cell targeting in rheumatoid arthritis and other autoimmune diseases. Nat Rev Immunol 2006;6:394-403.

74 Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety or rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomised, double-blind, placebo-controlled dose-ranging trial. Arthritis Rheum 2006;54:1390-400.

75 Looney RJ, Anolik JH, Campbell D, et al. B-cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum 2004;50:2580-9.

76 Pijpe J, Meijer JM, Bootsma H, et al. Clinical and histological evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjögren's syndrome. Ann Rheum Dis 2009;68:284-5.

77 Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren's syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5.

78 Carnahan J, Wang P, Kendall R, et al. Epratuzumab, a humanized monoclonal antibody targeting CD22: characterization of in vitro properties. Clin Cancer Res 2003;9(10 Pt 2):3982S-90S.

79 Steinfeld SD, Tant L, Burmester GR, et al. Epratuzumab (humanized anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phaseI/II study. Arthritis Res Ther 2006;8:R129.

80 Pers JO, d'Arbonneau F, Devauchelle-Pensec V, et al. Is periodontal disease mediated by salivary BAFF in Sjögren's syndrome? Arthritis Rheum 2005;52:2411-4.

81 Szodoray P, Jellestad S, Alex P, et al. Programmed cell death of peripheral blood B-cells determined by laser scanning cytometry in Sjögren's syndrome with a special emphasis on BAFF. K Clin Immunol 2004; 24:600-11.

82 Ramanujam M, Davidson A. The current status of targeting BAFF/BLyS for autoimmune diseases. Arthritis Res Ther 2004; 6:197-202.

83 Baker KP, Edwards BM, Main SH, et al. Generation and characterisation of LymphoStat-B, a human monoclonal antibody that antagonises the bioactivities of B lymphocyte stimulator. Arthritis Rheum 2003;48:3253-65.

84 Szodoray P, Jonsson R. The BAFF/APRIL system in systemic autoimmune diseases with a special emphasis on Sjögren's syndrome. Scand J Immunol 2005;62:421-8.

85 Lavie F, Miceli-Richard C, Ittah M, et al. Increase of B-cell-activating factor of the TNF family (BAFF) after rituximab treatment: insights into a new regulating system of BAFF production. Ann Rheum Dis 2007;66:700-3.

86 Ramos-Casals M, Brito-Zeron P, Yague J, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2005;44:89-94.

87 Wolfe GI, Nations SP, Burns DK, et al. Benefit of IVIG for long-standing ataxic sensory neuronopathy with Sjögren's syndrome. Neurology 2003;61:873.

88 Gorsin KC, Natarajan N, Ropper AH, et al. Rituximab treatment in patients with IVIg-dependant immune polyneuropathy: a prospective pilot trial. Muscle Nerve 2007;35:66-9.

89 Ferri C, Mascia MT. Cryoglobulinemic vasculitis. Curr Opin Rheumatol 2006;18:54-63.

90 Voulgarelis M, Dafni UG, Isenberg DA, et al. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's syndrome. Arthritis Rheum 1999;42:1765-72.

91 Bowman SJ, Booth DA, Platts RG. Measurement of fatigue and discomfort in primary Sjögren's syndrome using a new questionnaire tool. Rheumatology 2004;43:758-64.

92 Oxholm P. Primary Sjögren's syndrome-clinical and laboratory markers of disease activity. Semin Arthritis Rheum 1992;22:114-26.

93 Seror R, Rauvaud P, Bowman SJ, et al. EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): development of a consensus systemic disease activity index in primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

Chapter 4

Treatment of primary Sjögren's syndrome with rituximab

Chapter 4.1

Effective rituximab treatment in primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled trial

Jiska M Meijer[1], Petra M Meiners[1], Arjan Vissink[1], Fred KL Spijkervet[1], Wayel H Abdulahad[2], Nicole Sillevis Smitt-Kamminga[3], Liesbeth Brouwer[2], Cees GM Kallenberg[2], Hendrika Bootsma[2]

Departments of [1]Oral and Maxillofacial Surgery, [2]Rheumatology and Clinical Immunology, and [3]Opthalmology, University of Groningen, University Medical Center Groningen, The Netherlands

Arthritis and Rheumatism 2010; 62(4):960-968

ABSTRACT

Objective. To study the efficacy and safety of B-cell depletion with rituximab, a chimeric murine/human anti-CD20 monoclonal antibody, in patients with primary Sjögren's syndrome (pSS) in a double-blind, randomised, placebo-controlled trial.

Methods. Patients with active pSS, as determined by the revised American-European Consensus Group criteria, and a stimulated whole salivary flow rate of $\geq$0.15 mL/minute were treated with either rituximab (1000 mg) or placebo infusions at days 1 and 15. Patients were assigned randomly to a treatment group in a ratio of 2:1 ratio (rituximab:placebo). Follow-up was conducted at 5, 12, 24, 36 and 48 weeks. The primary endpoint was stimulated whole salivary flow rate, while secondary endpoints included functional, laboratory, and subjective variables.

Results. Thirty patients with pSS (29 female) were randomly allocated to a treatment group. The mean$\pm$SD age of the patients receiving rituximab was 43$\pm$11 years and the disease duration was 63$\pm$50 months, while patients in the placebo group were age 43$\pm$17 years and had a disease duration of 67$\pm$63 months. In the rituximab group, significant improvements, in terms of the mean change from baseline compared with that in the placebo group, were found for the primary endpoint of the stimulated whole saliva flow rate (p=0.038 versus placebo) and also for various laboratory parameters (B-cells and rheumatoid factor (RF) levels), subjective parameters (multidimensional fatigue inventory (MFI) scores and visual analogue scale (VAS) scores for sicca symptoms), and extraglandular manifestations. Moreover, in comparison with baseline values, rituximab treatment significantly improved the stimulated whole saliva flow rate (p=0.004) and several variables (e.g., B-cell and RF levels, unstimulated whole salivary flow rate, lacrimal gland function on lissamine green test, MFI scores, Short Form-36 health survey (SF-36) scores, and VAS scores for sicca symptoms). One patient developed mild serum sickness-like disease.

Conclusions. These results indicate that rituximab is an effective and safe treatment strategy for patients with pSS.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by chronic inflammation of the salivary and lacrimal glands, resulting in xerostomia and keratoconjunctivitis sicca in about 95% of patients.[1] These symptoms are frequently accompanied by extraglandular manifestations such as Raynaud's phenomenon, arthritis, arthralgia, and myalgia, and 85% of the patients experience severe fatigue. Moreover, B-cell hyperactivity, reflected by increased serum levels of IgG and rheumatoid factor (RF) and the presence of anti-SSA and anti-SSB autoantibodies, is a common finding in SS. Furthermore, SS has a large impact on health-related quality of life, employment, and disability as reflected by lower SF-36 scores, reduced employment rates, and higher rates of disability patients with SS compared with the general population.[1]

To date, no targeted systemic treatment has been available for SS. In pilot trials, however, it has been shown that rituximab, a chimeric murine/human anti-CD20 monoclonal antibody that binds to the B-cell surface antigen CD20, might improve subjective and objective symptoms related to primary SS (pSS) for at least 6 to 9 months.[2,3] On the basis of these promising results, a randomised, double-blind, placebo-controlled trial was performed to investigate the efficacy and safety of rituximab in the treatment of patients with pSS.

PATIENTS AND METHODS

Study design

This was a prospective, single-center, randomised, double-blind, placebo-controlled study. The study protocol was approved by the institutional review board of the University Medical Center Groningen. All patients provided their written informed consent.

Patients

All patients were ≥18 years and fulfilled the American-European Consensus Group criteria for pSS.[4] Eligibility criteria were a stimulated whole salivary flow rate of ≥0.15 mL/minute and positivity for autoantibodies (RF≥10 kIU/L and anti-SSA and/or anti-SSB autoantibodies). In addition, results form a salivary gland biopsy performed within 12 months before inclusion and showing the characteristic features of SS had to be available.[5] During the study, patients were asked to use reliable methods of contraception. Patients who had been treated previously with other biological disease-modifying antirheumatic drugs (DMARDs) were excluded. Treatment with prednisone and hydroxychloroquine had to be discontinued at least 1 month before baseline, and treatment with methotrexate, cyclophosphamide, cyclosporine, azathioprine, and other traditional DMARDs had to be discontinued at least 6 months before baseline. Patients were allowed to use artificial tears and artificial saliva, but the regimen had to remain identical

during follow-up. The use of these substitutes had to be stopped 1 day prior to each assessment.

All patients underwent electrocardiography and chest radiography at baseline. Patients with a history of any malignancy or with underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases, or immune deficiency were excluded.

Drug administration

Twenty patients were treated with intravenous (IV) infusions of 1000 mg rituximab (Roche, Woerden, The Netherlands) and 10 patients were treated with IV infusions of placebo on days 1 and 15. To minimise side effects (infusion reactions, serum sickness), all patients were pretreated with methylprednisolone (100 mg IV), acetaminophen (1000 mg orally), and clemastine (2 mg IV), and received 60 mg oral prednisone on days 1 and 2, 30 mg on days 3 and 4, and 15 mg on day 5 after each infusion.

Outcome parameters

Definition of endpoints. The primary endpoint was defined as a significant improvement of the secretion of stimulated whole saliva (flow rate mL/minute) in the rituximab group compared with the placebo group. Secondary endpoints were measurements of salivary/lacrimal function and immunologic and subjective variables. All variables were assessed at baseline (within 4 weeks before treatment), and at 5, 12, 24 and 48 weeks after treatment.

Determination of salivary gland function. Whole, parotid and submandibular/sublingual saliva samples were collected in a standardised manner and at a fixed time of the day (in this study between 1:00 and 4:00 PM), in order to minimise fluctuations related to a circadian rhythm of salivary secretion[6,7] and composition. Glandular saliva was collected from both individual parotid glands by use of Lashley cups, and submandibular/sublingual saliva was collected simultaneously by syringe aspiration from the area with the orofices of the submandibular excretory ducts. Unstimulated saliva was collected the first 5 minutes, followed by collection of stimulated saliva for 10 minutes. The salivary glands were stimulated by citric acid solution (2%), applied with a cotton swab to the lateral borders of the tongue every 30 seconds. Flow rates were calculated and the composition of saliva was analysed according to the methods described by Burlage et al and Kalk et al.[8-10]

Determination of lacrimal gland function. Lacrimal gland function was evaluated by performing a Schirmer's test, a lissamine green (LG) test and tear break-up time (TBUT).[11] Schirmer's test (without anesthesia) was carried out by placing a filter strip in the lower fornix of the conjunctiva of the eye. The amount of wetting was measured after 5 minutes. The LG test was performed by instillation of 1% LG in both eyes. After 1 or 2 full blinks, the intensity of staining of both medial and lateral bulbar conjunctiva and the

cornea was scored, with a maximum score of 9 points (up to 3 points for each section (1 = sparsely scattered, 2 = densely scattered, 3 = confluent)). The TBUT is the interval between a complete blink and the appearance of the first randomly distributed dry spots and is assessed by instilling a 1% fluorescein solution in the fornix of both eyes. The patient was asked to blink a few times, after which the interval in seconds between the last blink and the first blink in the tear film was measured.

Laboratory assessments. Laboratory assessments included serum biochemical analysis and determination of the complete blood cell count. Levels of immunoglobulins (IgG, IgA and IgM) and RF were measured by nephelometry. Numbers of circulating CD19+, CD4+ and CD8+ T-cells were quantified with the use of a FACSCalibur flow cytometer in TruCOUNT™ tubes (Becton Dickinson, Mountain View, CA). The absolute T-cell number was determined by comparing the number of cellular events with that of bead events, analysed using CellQuest software (Becton Dickinson).

Subjective assessments. Patients completed the Multidimensional Fatigue Inventory (MFI)[12] and the Short Form-36 health survey (SF-36).[13] In addition, a 100-mm visual analogue scale (VAS) was used for rating oral and ocular sicca symptoms.

Extraglandular manifestations. Arthralgia, arthritis, renal involvement, esophageal involvement (confirmed by esophageal scintigraphy), polyneuropathy, Raynaud's phenomenon, tendomyalgia, and vasculitis were defined as extraglandular manifestations. At each visit, extraglandular manifestations were scored as present or not present, according to protocol.

Definition of serum sickness. Serum sickness was defined as development of fever, lymph node swelling, purpura, myalgia, arthralgia, thrombocytopenia, and proteinuria, as well as a decrease in complement levels. Serum sickness-like disease was defined as the development of some of these symptoms of serum sickness.

Sample size

Based on a formal sample size calculation, 30 patients were included, of whom 20 were assigned to receive rituximab and 10 to receive placebo. The patients were randomly assigned by staff in the pharmacy department to 1 of the 2 treatment arms in a 2:1 ratio (rituximab:placebo) in blocks of 3, using a random-number generator on a computer. The study investigators (who also provided care and assessed the outcome variables) and patients were blinded to the assigned study medication. The code was revealed to the investigators after follow-up of all patients was completed. Because of the double-blind design, we assumed a 5% rate of false-positive findings among the patients in the placebo group who displayed clinical signs of serum sickness. This resulted in an obligation to terminate the trial if 2 patients developed clinical signs of serum sickness after the first or second infusion within the first 9 patients, or if 3 patients developed clinical signs of serum sickness after the first or second infusion within the first 29 patients. If, for any reason, the protocol was terminated, patients were not replaced.

Table 1. Baseline characteristics of the patients in the rituximab and placebo treatment groups.[#]

Variable	Placebo (n=10)	Rituximab (n=20)
Age, mean±SD years	43±17	43±11
No. female/no. male	10/0	19/1
Disease duration, mean±SD months	67±63	63±50
IgG, mean±SD gm/liter	21±7	23±8
RF, mean±SD kIU/L	221±245	102±79
Anti-Ro/SSA positive	10 (100)	20 (100)
Anti-La/SSB positive	8 (80)	14 (70)
Parotid gland swelling	10 (100)	17 (85)
Whole salivary flow, mL/minute		
Unstimulated	0.06±0.09	0.17±0.19*
Stimulated	0.42±0.26	0.70±0.57
Extraglandular manifestations		
Arthralgia	5 (50)	15 (75)
Arthritis	0 (0)	6 (30)
Renal involvement	0 (0)	2 (10)
Esophageal involvement	1 (10)	0 (0)
Peripheral polyneuropathy	0 (0)	1 (5)
Raynaud's phenomenon	6 (60)	11 (55)
Tendomyalgia	8 (80)	17 (85)
Vasculitis	3 (30)	6 (30)
Thyroid dysfunction	0 (0)	1 (5)
Use of artificial tears	8 (80)	14 (70)
Use of artificial saliva	2 (20)	2 (10)

[#]Except where indicated otherwise, values are the number (%) of patients. RF, rheumatoid factor. *=p<0.05 versus placebo.

Statistical analyses

All data analyses were carried out according to a preestablished plan. To compare treatment effects over time between the 2 treatment groups, repeated-measures analysis of variance was performed. To determine whether an improvement had occurred over time relative to baseline, repeated-measures analysis of covariance was performed to evaluate changes from baseline. Statistical analyses performed on secondary endpoints were considered to be of explorative in nature, and therefore no corrections were made for multiple comparisons. The assumptions on data homogeneity were met. If data were not normally distributed, a log-transformation was performed on the data prior to statistical analysis, or a distribution-free alternative was used.

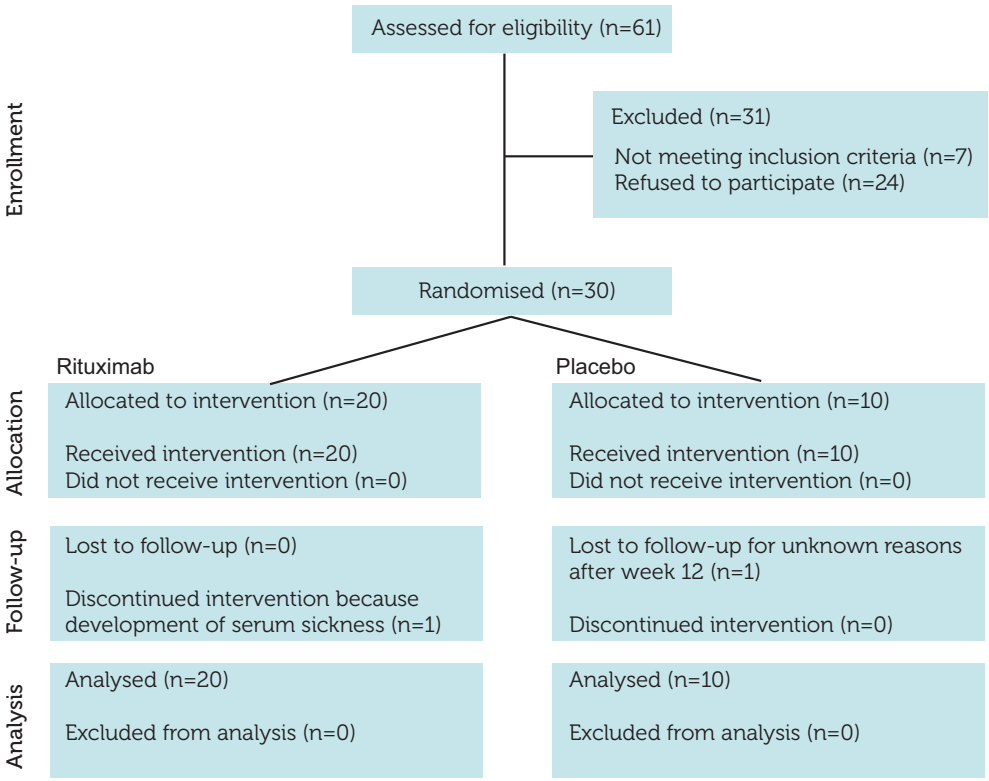

Figure 1. Randomisation of patients with primary Sjögren's syndrome to 1 of the 2 treatments groups in the randomised, double-blind, placebo-controlled trial of rituximab. Of a cohort of 300 patients, a preselection of 61 patients was made, based on last available sialometry, IgG, anti-SSA positivity, anti-SSB positivity, and RF data.

RESULTS

Patient distribution

Between August 2006 and September 2007, 30 patients were randomly assigned to a treatment group (figure 1). The baseline characteristics of the patients are summarized in table 1. Six patients were taking medication that had to be discontinued before study inclusion, in accordance with the inclusion criteria.

Efficacy (table 2)

Salivary gland function. Stimulated whole salivary flow rate (the primary endpoint) (figure 2A) significantly improved in the rituximab group ($p=0.018$ at week 5 and $p=0.004$ at week 12, versus baseline), while in the placebo group these values significantly decreased from baseline, which is consistent with the natural progression of the disease. A significant difference in the mean change from baseline to week 12 in the stimulated

Table 2. Results of laboratory, functional, and subjective assessments in the rituximab and placebo treatment groups.[§]

Variable	Baseline		Week 5		Week 12		Week 24		Week 36		Week 48	
	Placebo	Rituximab	Placebo	Rituximab	Placebo	Rituximab	Placebo	Rituximab	Placebo	Rituximab	Placebo	Rituximab
UWS, mL/minute[$]	0.06±0.09 (0.03)	0.17±0.19 (0.08)	0.09±0.07 (0.08)	0.24±0.22 (0.20)*	0.05±0.05 (0.04)	0.23±0.22 (0.19)*	0.08±0.08 (0.09)	0.22±0.25 (0.14)	0.07±0.09 (0.02)	0.16±0.15 (0.11)	0.05±0.04 (0.04)*	0.18±0.18 (0.13)
SWS, mL/minute[$]	0.42±0.26 (0.36)	0.70±0.57 (0.47)	0.41±0.24 (0.37)	0.84±0.71 (0.48)*	0.28±0.17 (0.25)*	0.87±0.87 (0.56)*#	0.36±0.28 (0.24)	0.74±0.60 (0.52)	0.29±0.18 (0.26)*	0.64±0.58 (0.44)	0.28±0.21 (0.22)*	0.66±0.71 (0.42)
Schirmer's test, mm/5 minutes[$]	7±9 (3)	11±11 (7)	7±11 (4)	10±9 (10)	6±5 (5)	11±10 (11)	8±8 (6)	12±12 (5)	7 ±7 (5)	11 ±10 (7)	5±5 (6)*	10±11 (7)
LG test[$]	4±1 (4)	3±2 (4)	5±1 (5)	3±2 (3)*	4±2 (4)	3±2 (3)*	4±2 (4)	2±2 (2)*	4 ±2 (4)	2 ±2 (2)*	4±2 (4)	2±3 (1)*
TBUT, seconds[$]	3±2 (3)	6±2 (6)	3±1 (3)	6±3 (6)	3±2 (3)	5±3 (5)	5±2 (6)*	6±3 (7)	5 ±3 (5)*	7 ±3 (8)*	4±3 (4)	6±3 (8)
B-cells, 10^9/L[$]	0.27±0.12 (0.28)	0.21±0.17 (0.18)	0.20±0.09 (0.17)*	0.00±0.00 (0.00)*#	0.25±0.10 (0.27)	0.01±0.03 (0.00)*#	0.28±0.11 (0.26)	0.05±0.08 (0.03)*#	0.28 ±0.12 (0.31)	0.10 ±0.08 (0.08)*#	0.33±0.15 (0.37)	0.17±0.10 (0.15)*#
RF, kIU/L[$]	221±245 (108)	102±79 (83)	162±175 (96)*	55±36 (53)*	156±138 (102)	44±30 (36)*#	258±260 (113)	45±34 (32)*#	253 ±256 (119)	71 ±68 (54)*#	225±199 (126)	103±103 (72)
MFI, general fatigue	14±5 (17)	16±4 (18)	11±5 (12)*	15±4 (16)	13±5 (14)	13±4 (13)*	12±5 (12)	13±4 (12)*	14 ±4 (14)	14 ±4 (14)	14±6 (17)	15±4 (16)
SF-36 total score	64±17 (65)	52±20 (53)	70±17 (70)	56±18 (52)	67±15 (71)	63±15 (65)*	72±16 (82)	67±16 (70)*	63 ±16 (65)	60 ±17 (64)*	62±17 (62)	55±18 (55)
VAS oral dryness	59±28 (62)	55±28 (61)	50±28 (53)	47±27 (53)*	53±30 (60)	40±27 (40)*	64±27 (74)	34±27 (46)*	68 ±26 (79)	51 ±28 (61)*	69±25 (76)	50±28 (53)*
VAS ocular eyes	65±27 (63)	59±29 (68)	55±28 (52)	49±28 (51)*	61±25 (54)	48±29 (47)*	68±24 (74)	41±28 (43)*	70 ±27 (72)	46 ±27 (52)*#	76±19 (80)	46±28 (55)*#

[§] Values are the mean±SD (median). Due to missing data, the differences between mean values in this table differ slightly from the means of differences shown in figure 2.
* P<0.05 versus baseline in the same treatment group, by analysis of covariance.
# P<0.05 versus change from baseline in the placebo group.
UWS, unstimulated whole salivary flow rate; SWS, stimulated whole salivary flow rate; LG, lissamine green; TBUT, tear break-up time; RF, rheumatoid factor; MFI, Multidimensional Fatigue Inventory; SF-36, Short Form 36; VAS visual analogue scale [$] Data are not normally distributed.

whole salivary flow rate was found between the groups (p=0.038). The unstimulated whole salivary flow rate (figure 2B) and the submandibular/sublingual flow rate (results not shown) also significantly increased from baseline in the rituximab group.

Lacrimal gland function. The LG test showed significant improvement in lacrimal gland function in the rituximab group from baseline to weeks 5 to 48. However, the Schirmer's test and TBUT revealed no significant changes in lacrimal gland function in either group.

Laboratory assessments. B-cells were completely depleted after the first infusion in patients treated with rituximab (figure 2C). In contrast, no significant changes in the mean absolute number of B-cells were found in the placebo group. In the patient who developed mild serum sickness-like disease (see safety assessments below), who received only 1 infusion of rituximab, B-cells reappeared within 12 weeks after treatment. In the other 19 rituximab-treated patients, B-cells returned within 24 to 48 weeks after treatment, although B-cell levels still had not returned to baseline by week 48. Significant differences in the mean change in absolute B-cell counts from baseline to weeks 5, 12, 24, 36 and 48 were found between the groups ($p<0.05$). No significant changes were found in the levels of CD4+ and CD8+ T-cell levels in either the rituximab group or placebo group. Levels of RF (figure 2D) decreased significantly in the rituximab group over weeks 5 to 36, whereas in the placebo, the RF levels decreased signifcantly only at week 5. Significant differences in the mean change in RF levels from baseline between the groups were at weeks 5, 12, 24 and 36 (each $p<0.05$). The same patterns of change were found for the levels of IgG, IgM and IgA in each group (results not shown).

Changes in subjective assessments. The MFI and SF-36 scores showed the strongest improvements in the rituximab group (figures 2E and 2F). Compared with that in the placebo group, patients receiving rituximab showed a significant change in MFI score, showing decreased scores for reduced activity from baseline at week 36 (p=0.023) and for reduced motivation from baseline at week 12 (p=0.039). In addition, in patients receiving rituximab, there was significant improvement in the SF-36 score for vitality from baseline at week 36 (p=0.013). Moreover, all VAS scores for oral and ocular sicca symptoms improved in the rituximab group (table 2 and figures 2G and 2H), whereas VAS scores in the placebo group only showed a significant improvement at week 5. Significant differences in mean change in VAS scores from baseline were observed between the groups, in that patients receiving rituximab reported improvement in the ratings for dry mouth during the at weeks 24, 36 and 48 and in the ratings for dry eyes at weeks 36 and 48 (each $p<0.05$).

Extraglandular manifestations. At baseline, there were no differences in the number of extraglandular manifestations between the rituximab group and the placebo group (figure 2I). The number of reported extraglandular manifestations (number reported as present) significantly decreased in the rituximab group compared with the placebo for tendomyalgia at weeks 12 and 36 (p=0.029) and for vasculitis at week 24 (p=0.030). In addition, there was a strong tendency toward a significant decrease in the number

Table 3. Adverse events observed in patients following treatment with rituximab as compared with placebo. [#]

Events		Placebo (n=10)	Rituximab (n=20)
Early infusion reaction		0	2 (10)
Late infusion reaction		0	2 (10)
Serum sickness		0	1 (5)
Infections within 2 weeks after infusion	Upper airway infection		1 (5)
	Parvovirus		1 (5)
Infections during 48 weeks of follow-up	Otitis media		2 (10)
	Upper airway infection	4 (40)	4 (20)
	Recurrence of ocular toxoplasmosis		1 (5)
	Parotid gland infection		3 (15)
	Recurrence of herpes zoster	1 (10)	
	Epstein-Barr virus	1 (10)	
	Rubella	1 (10)	

[#] Values are the number (%) of patients.

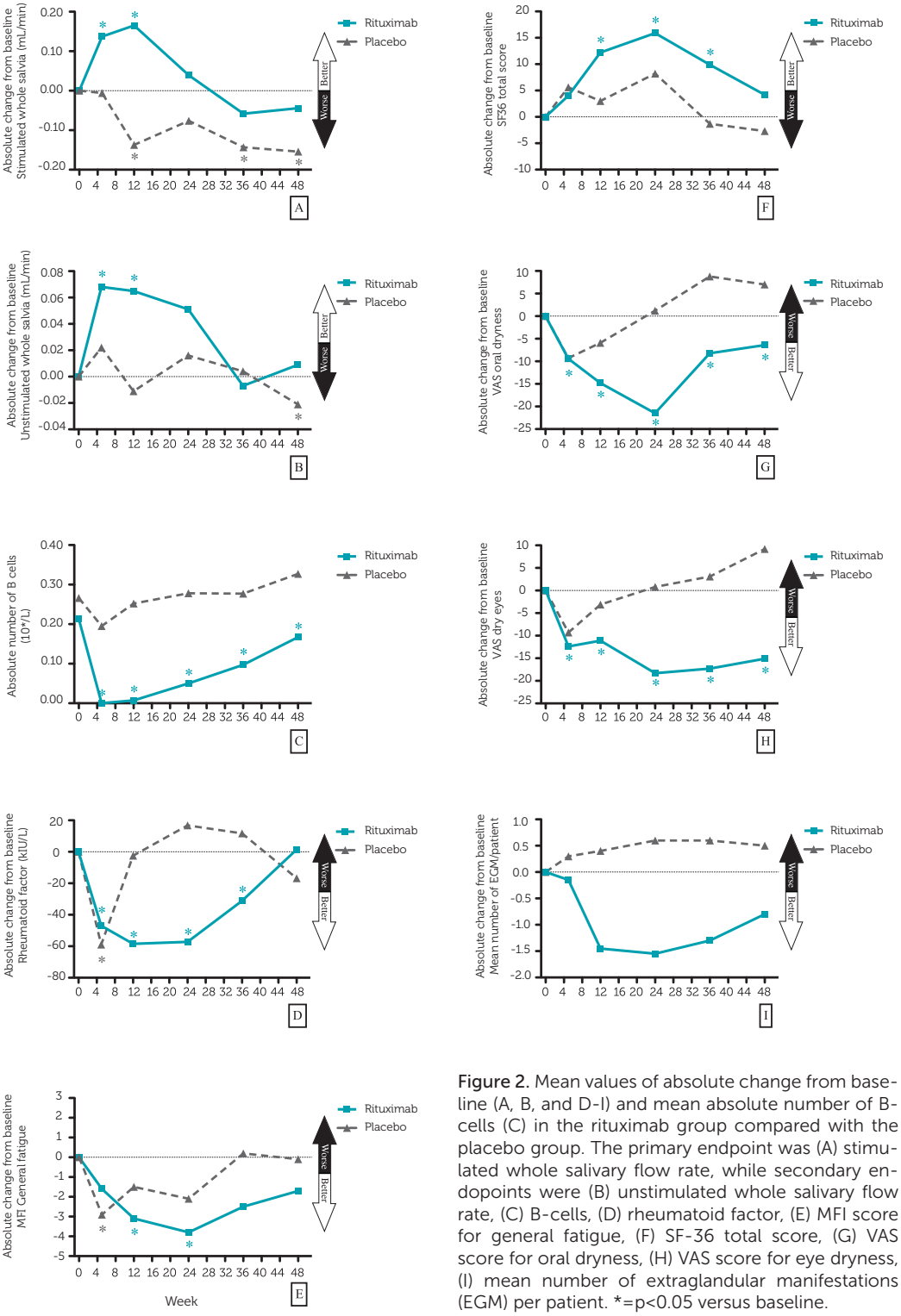

Figure 2. Mean values of absolute change from baseline (A, B, and D-I) and mean absolute number of B-cells (C) in the rituximab group compared with the placebo group. The primary endpoint was (A) stimulated whole salivary flow rate, while secondary endopoints were (B) unstimulated whole salivary flow rate, (C) B-cells, (D) rheumatoid factor, (E) MFI score for general fatigue, (F) SF-36 total score, (G) VAS score for oral dryness, (H) VAS score for eye dryness, (I) mean number of extraglandular manifestations (EGM) per patient. *=p<0.05 versus baseline.

of reported symptoms of Raynaud's phenomenon (p=0.057), tendomyalgia (p=0.074), and arthralgia (p=0.058) from baseline to week 24 in patients receiving rituximab. Six patients in the rituximab group had symptoms of arthritis at baseline; this resolved in 4 patients during follow-up. In the placebo group, no patients had symptoms of arthritis at baseline; however, 3 patients developed symptoms during follow-up. One patient with decreased thyroid function before rituximab treatment showed a normalization of thyroid function without additional thyrostatic supplementation. Renal function remained stable during follow-up (2 patients had renal tubular acidosis, and both were treated with rituximab). Clinical symptoms of polyneuropathy (in 1 patient in the rituximab group) improved after 12 weeks of follow-up.

Safety (table 3)

Serum sickness. One female patient with diabetes developed a mild serum sickness-like disease, which was identified 14 days after the first infusion of rituximab. The patient developed fever, purpura on both legs, and arthralgia, and she was admitted to the hospital in order to control her serum glucose levels during administration of IV administration of corticosteroids and nonsteroidal anti-inflammatory drugs. She recovered completely within a few days, without developing human antichimeric antibodies. The second infusion of rituximab was not administered. This patient had not been treated with any immunosuppressive drug previously. None of the 6 patients who had discontinued immunosuppressive drugs 1 to 6 months prior to rituximab treatment developed serum sickness-like disease.

Infections. A total of 12 infections were reported by 11 patients in the rituximab group, while 4 patients in the placebo group reported a total of 7 infections. The rates of infection were 76 and 65 events per 100 patient-years for the placebo and rituximab groups, respectively. None of the infections required hospitalisation. No opportunistic infections were seen.

DISCUSSION

This study showed that rituximab-induced B-cell depletion can be considered an effective and safe treatment strategy for patients with pSS. B-cell depletion resulted in improvement of objective and subjective parameters of disease activity in pSS patients for at least 6 to 9 months. Amongst the endpoints, salivary function improved, fatigue diminished and the number of extraglandular manifestations was reduced.

Rituximab has already been shown to be a safe and effective treatment for rheumatoid arthritis (RA), as shown by a decrease in disease activity, diminished radiological progression of the disease and an improved quality of life in patients with RA.[14-16] Previously, the utility of rituximab for the treatment of SS had only been investigated in a few

open-label, phase II studies and 1 randomised, double-blind, placebo-controlled study. Results from open-label studies, in terms of objective and subjective variables, were promising,[2,3] as was the improvement of systemic features.[17] Although the duration of treatment effect differed between the trials, in all trials a significant effect occurred 12 to 24 weeks after treatment. In a previous randomised, double-blind, placebo-controlled study of rituximab treatment of SS, a significant improvement in fatigue (the primary endpoint) was noted compared with the values at baseline in the rituximab group, but there were no significant changes in secondary endpoints assessing glandular manifestations (unstimulated salivary flow rate and Schirmer's test results).[18] Moreover, the study by Dass et al[18] used an objective eye test for lacrimal gland function that was less accutate (the Schirmer's test); the Rose Bengal score and LG test are considered to be more accurate.[11] This fact together with the small number of patients included in that trial (8 receiving rituximab, 9 receiving placebo), might explain the lack of significant improvement in glandular manifestations following rituximab treatment.

In our trial, most significant improvements in the endpoints associated with rituximab treatment were observed between 12 weeks and 36 weeks following treatment. In contrast, improvement of most of the variables observed in the placebo group occurred 5 weeks after the first infusion. We hypothesize that the improvements observed after placebo treatment were related to the prednisolone, which had been administered before and during the days after the infusions, although data are inconclusive regarding the effect of prednisolone on SS symptoms. Although one study reported a significant increase in whole saliva flow during the use of low-dose prednisolone,[19] other studies noted no significant improvement in glandular function.[20,21]

The stimulated whole salivary flow rate provides a general indication of overall salivary glandular function, which is an important outcome in a disease that specifically affects the salivary glands. Pijpe et al[3] reported the occurrence of a significant increase in the stimulated whole salivary flow rate in rituximab-treated patients with pSS whose stimulated salivary flow rate was >0.10 mL/minute at baseline. These patients also showed significant improvement in such subjective parameters as mouth dryness, arthralgia, physical functioning, vitality, and most domains of the MFI. In other words, patients with some residual secretory potential may benefit the most from rituximab treatment. The secretory potential at baseline might even be used to identify those patients who would be considered to be a good responder to rituximab treatment. Therefore, the stimulated whole salivary flow rate was chosen as the primary endpoint of our study. As a cutoff value, a stimulated whole salivary flow rate of ≥0.15 mL/minute was chosen, since this is a flow rate that discriminates patients showing increasing disease activity (e.g., progressive loss of secretory function) and patients with an end-stage pSS.[21] In our study, we observed an increase in salivary flow in the rituximab group that exceeded the intrapatient variability observed for repeated collections of saliva.[8] This increase was also reflected in the improvements of subjective scores for dry mouth, which indicates that

these changes were clinically meaningful in the patients. The, nonsignificant baseline difference between the groups for the stimulated whole salivary flow rate was caused by high salivary flow rates in a few patients before inclusion. All patients in the study were required to have a stimulated whole salivary flow of ≥0.15 mL/minute. This meant that all patients had a clinically relevant functional secretory salivary gland capacity. Our pilot study revealed that no relevant improvement in salivary gland function can be expected in patients with little or no secretory potential at baseline.

In clinical trials of rituximab in patients with RA, the number of reported (serious) infections and infusion reactions is within the range expected for patients with RA treated with biological DMARDs. Therefore, the risk:benefit ratio is considered to be good regarding rituximab treatment of RA.[22] In clinical trials of rituximab treatment of other autoimmune diseases (including SS), the reported numbers of infusion reactions and infections vary widely; this is possibly due to variability in how these adverse events are defined or to small numbers of patients. The incidence of infusion reactions and infections reported for the rituximab group in this trial was largely comparable with that in the placebo group, and was lower or within the same range as that reported previously.[23] Moreover, the rate of infections per 100 patient-years was lower compared with the previously reported rate in RA patients treated with rituximab. This might be explained by the fact that our patients did not have any other immunosuppressive therapy.[24]

When compared with patients with lymphoma, patients with RA and patients with systemic lupus erythematosus (SLE) treated with rituximab, patients with pSS treated with rituximab develop serum sickness(-like) disease more frequently (6 to 27%).[25] A therapy-related explanation for this phenomenon might be that patients with RA and those with SLE usually receive or have received higher doses of steroids and/or other immunosuppressive drugs, in addition to rituximab, whereas our patients with pSS received no other medication, except a 5-day period of steroids after administration of rituximab. Another therapy-related explanation is that patients with RA and those with SLE have been exposed to intensive immunosuppressive regime, including treatment with biological DMARDs, before they undergo treatment with rituximab, whereas our patients with pSS were far more likely to have never taken such medications at the time of rituximab treatment. The higher susceptibility for serum sickness could also be inherent to the disease itself. The patients with pSS in this trial, as well as in our pilot trial,[3] who developed serum sickness were more likely to have an active, early, and progressive form of SS. It is possible that such patients with pSS are more prone to develop serum sickness. Furthermore, hypergammaglobulinaemia is common in pSS, which could make these patients prone to the development and deposition of immune complexes and, thus, to serum sickness(-like) disease.[18]

Because of the higher risk of developing serum sickness(-like) disease in patients with SS, we decided to increase the steroid dose. Only 1 patient in the current study developed serum sickness-like disease (5%), which is considerably lower than the incidence

reported in our open-label study (27%).[3] Based on these findings, we would recommend administering 100 mg methylprednisolone immediately prior to each infusion of rituximab. The oral regimen of prednisolone in the days following each infusion is a point of interest and should be explored in future trials. The administration of higher doses of prednisolone in the days following infusion, such as is performed during lymphoma treatment, should also be considered.

This study indicates that rituximab treatment could be effective for patients who have active pSS and remaining salivary gland secretory potential, as well as for pSS patients with extraglandular manifestations. Future trials of rituximab treatment for patients with pSS are warranted, in which larger groups of patients should be included and less strict inclusion criteria (e.g., no restriction to salivary gland function ≥0.15 mL/minute and autoantibody positivity) should be used, in order to be able to extrapolate the results to a larger group of patients with pSS. In addition to the defined inclusion criteria, attention should be given to the criteria used for response to treatment. Activity scores for pSS have now been developed and need validation. These scores should be included in the response criteria to be used in future trials.

Based on the promising results of this study and on our study on retreatment with rituximab, which resulted in a beneficial effect comparable to that of the first treatment with this biological agent,[26] a maintenance therapy with rituximab infusions every 6 to 9 months may be a reasonable approach. Advantages of maintenance therapy might be a reduction or even arrest of disease progression and improvement of health-related quality of life for a long period. This improvement will be a great achievement in patients with SS, since SS has a large impact on health-related quality of life, employment and disability.[1] A threat might be the, long-term side effects (thus-far unknown) of repeated B-cell depletion. The timing of retreatment could be based on return of symptoms; however, retreatment just before return of symptoms would even be better.

In conclusion, the results of this study indicate that rituximab could be an effective and safe treatment strategy for patients with pSS. B-cell depletion resulted in improvement of the primary endpoint, the stimulated whole salivary flow rate. Explorative analyses also showed improvements, of at least 6 to 9 months' duration, in the objective and subjective secondary endpoints of disease activity. Since SS has a great impact on health-related quality of life, employment and disability,[1] it is worthwhile to further explore the role of rituximab in a large-size, randomised, controlled trial.

ACKNOWLEDGEMENTS

We are grateful to Janita Kuiper, Philip M Kluin, Jaqueline E van der Wal, Khaled Mansour, Gustaaf W van Imhoff and Justin Pijpe for their support and meaningful discussions.

FUNDING

This trial was an investigator-driven study that was financially supported by Roche (Woerden, The Netherlands), which also supplied study medication. There was no involvement of the study sponsor in the study design, patient recruitment, data collection, analysis and interpretation of the data, or writing of the report. Statistical analyses were performed by the statistical department of Xendo Drug Development BV (Groningen, The Netherlands), which is an independent contract research organisation. Medical writing support was provided by staff at Adelphi Communications (supported by F Hoffmann-La Roche Ltd) during the final preparation of this article.

References

1 Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology (Oxford) 2009;48:1077-82.

2 Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007;57:310-7.

3 Pijpe J, van Imhoff GW, Spijkervet FKL, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005;52:2740-50.

4 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.

5 Pijpe J, Kalk WWI, van der Wal JE, et al. Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46:335-41.

6 Dawes C. Circadian rhythms in human salivary flow rate and composition. J Physiol 1972;220:529-45.

7 Ferguson DB, Fort A, Elliott AL, et al. Circadian rhythms in human parotid saliva flow rate and composition. Arch Oral Biol 1973;18:1155-73.

8 Burlage FR, Pijpe J, Coppes RP, et al. Accuracy of collecting stimulated human parotid saliva. Eur J of Oral Sci 2005;113:386-90.

9 Kalk WW, Vissink A, Stegenga B, et al. Sialometry and sialochemistry: a non-invasive approach for diagnosing Sjögren's syndrome. Ann Rheum Dis 2002;61:137-44.

10 Kalk WWI, Vissink A, Spijkervet FKL, et al. Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome. Ann Rheum Dis 2001;60:1110-6.

11 Kalk WW, Mansour K, Vissink A, et al. Oral and ocular manifestations in Sjögren's syndrome. J Rheumatol 2002;29:924-30.

12 Smets EM, Garssen B, Bonke B, et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315-25.

13 Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.

14 Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomised, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793-806.

15 Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol 2008; 5:20-30.

16 Popa C, Leandro MJ, Cambridge G, et al. Repeated B-lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. Rheumatology 2007;46:626-30.

17 Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;64:913-20.

18 Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren's syndrome with rituximab: results of a randomised, double-blind, placebo controlled pilot study. Ann Rheum Dis 2008;67:1541-4.

19 Miyawaki S, Nishiyama S, Matoba K. Efficacy of low-dose prednisolone maintenance for saliva production and serological abnormalities in patients with primary Sjögren's syndrome. Intern Med 1999;38:938-43.

20 Fox PC, Datiles M, Atkinson JC, et al. Prednisone and piroxicam for treatment of primary Sjögren's syndrome. Clin Exp Rheumatol 1993;11:149-56.

21 Pijpe J, Kalk WWI, Bootsma H, et al. Progression of salivary gland dysfunction in patients with Sjögren's syndrome. Ann Rheum Dis 2007;66:107-12.

22 Fleischmann RM. Safety of biologic therapy in rheumatoid arthritis and other autoimmune

diseases: focus on rituximab. Semin Arthritis Rheum 2008.

23 Gurcan HM, Keskin DB, Stern JN, et al. A review of the current use of rituximab in autoimmune diseases. Int Immunopharmacol 2009;9:10-25.

24 Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum 2007;56:3896-908.

25 Meijer JM, Pijpe J, Bootsma H, et al. The future of biologic agents in the treatment of Sjögren's syndrome. Clin Rev Allergy Immunol 2007;32:292-7.

26 Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5.

Chapter 4.2

Efficacy of retreatment with rituximab in patients with primary Sjögren's syndrome

Petra M Meiners[1]*, Suzanne Arends[2]*, Jiska M Meijer[1,3], Rada V Moerman[2], Fred KL Spijkervet[1], Arjan Vissink[1], Hendrika Bootsma[2]

* Both authors contributed equally to this work

Departments of [1]Oral and Maxillofacial Surgery, [2]Rheumatology and Clinical Immunology, and [3]General Practice, University of Groningen, University Medical Center Groningen, The Netherlands

Submitted

In primary Sjögren's syndrome (pSS), 2 randomised controlled trials (RCT) showed significant improvement in objective and subjective measures after rituximab treatment.[1,2] A pilot study involving 5 pSS patients indicated that retreatment with rituximab results in similar response as found during initial treatment.[3] Recently, Gottenberg et al[4] found good physician-reported efficacy and tolerance during following courses of rituximab in 41 initially responding pSS patients.

To further study the efficacy of retreatment, we analysed data of pSS patients who received their first 2 courses of rituximab within our previously reported RCT[2] and following extension study.[5] Each course consisted of 1000 mg rituximab intravenously (given with 100 mg methylprednisolone) on days 1 and 15.

During both courses, patients were evaluated at baseline and at weeks 24 and 48. Assessments included EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)[6], stimulated whole salivary flow rate (SWS), B-cells, rheumatoid factor (RF), IgG levels, patient global disease activity (GDA), multidimensional fatigue inventory general fatigue (MFI-GF) and visual analogue scale (VAS) oral and ocular dryness (see references 2, 5 and 7 for details). Variables within patients were analysed using the Wilcoxon signed-rank test.

Fifteen patients (14 female) were included. Patients had median (range) age and disease duration of 39 years (27-65) and 37 months (3-154), respectively. Median interval between courses was 103 weeks (60-136).

Both courses of rituximab resulted in significant improvement of ESSDAI, B-cells, RF, IgG and MFI-GF at week 24 compared with baseline. Patient GDA and VAS oral dryness improved significantly during the first course and showed a trend for improvement during the second course. Improvement in VAS ocular dryness was observed only during the first course. All these variables, except for ocular dryness, showed significant deterioration at week 48 compared with week 24 during the first course. The same pattern was found during the second course, although deterioration seemed less pronounced. SWS remained stable during the first 24 weeks of both courses, but significant decrease was seen at week 48 of the first course (table 1). Absolute changes per patient over time during both courses are shown in figure 1.

Retreatment with rituximab was well-tolerated. One patient developed mild serum-sickness-like disease after the first infusion of both courses (second infusions were not administered).

The main strength of this analysis is no selection regarding initial response to rituximab. The main limitations are the small sample size and the varying time between courses, because retreatment was started after completion of the entire RCT and after recurrence of symptoms. No relation was found between the interval between courses and the effect of the second course.

In conclusion, retreatment with rituximab resulted in comparable beneficial effects as initial treatment on objective parameters, including ESSDAI, whereas the effect on patient-reported parameters was somewhat less pronounced. The latter finding is in line

Table 1. Clinical and laboratory parameters during the first and second course of rituximab in patients with pSS.

Parameter	Course	Week 0	Week 24	p Value[#]	Week 48	p Value[§]
ESSDAI	First	9.0 (4.0-13.0)	2.5 (0.0-9.0)	0.006	8.0 (2.0-17.0)	0.009
ESSDAI	Second	8.0 (2.0-18.0)	3.0 (0.0-10.0)	0.005	5.0 (1.0-26.0)	0.028
SWS (mL/minute)	First	0.47 (0.11-2.49)	0.52 (0.07-2.24)	0.694	0.37(0.07-2.95)	0.048
SWS (mL/minute)	Second	0.40 (0.02-1.47)	0.35 (0.06-1.72)	0.320	0.34 (0.04-1.69)	0.691
B-cells (10^9/L)	First	0.20 (0.01-0.40)	0.05 (0.00-0.31)	0.002	0.16 (0.05-0.31)	0.011
B-cells (10^9/L)	Second	0.22 (0.02-0.52)	0.00 (0.00-0.24)	0.001	0.15 (0.01-0.41)	0.002
RF (kIU/L)	First	88 (8-241)	30 (10-120)	0.001	72 (8-400)	0.003
RF (kIU/L)	Second	95 (12-230)	37 (13-160)	0.002	43 (11-354)	0.056
IgG (g/L)	First	22.9 (13.0-44.3)	19.3 (13.9-26.1)	0.001	21.4 (14.1-35.6)	0.004
IgG (g/L)	Second	22.2 (13.7-41.5)	18.9 (12.1-25.0)	0.002	18.3 (11.5-33.3)	0.320
Patient GDA	First	62 (43-74)	25 (0-61)	0.011	53 (4-84)	0.037
Patient GDA	Second	52 (15-93)	38 (0-85)	0.060	37 (3-82)	0.410
MFI-GF	First	16 (4-20)	12 (5-20)	0.016	16 (4-20)	0.081
MFI-GF	Second	16 (4-20)	13 (7-20)	0.019	15 (10-20)	0.168
VAS oral dryness	First	58 (0-91)	25 (0-67)	0.021	50 (0-88)	0.010
VAS oral dryness	Second	60 (1-92)	37 (0-84)	0.053	65 (1-88)	0.115
VAS ocular dryness	First	63 (0-88)	33 (0-89)	0.041	55 (0-90)	0.624
VAS ocular dryness	Second	55 (0-91)	53 (0-94)	0.802	59 (4-87)	0.463

Values are presented as median (range).
[#] p Value compared with values recorded at baseline.
[§] p Value compared with values recorded at week 24.
pSS, primary Sjögren's syndrome; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; SWS, stimulated whole salivary flow rate; RF, rheumatoid factor; GDA, global disease activity; MFI-GF, multidimensional fatigue inventory general fatigue; VAS, visual analogue scale.

with an earlier study in pSS.[8] Because goals of retreatment include maintenance of efficacy and prevention of flare, further studies are needed to investigate optimal timing of retreatment of rituximab in pSS patients.

ACKNOWLEDGEMENTS

We are grateful to Janita Bulthuis-Kuiper for her contribution to the data collection.

FUNDING

This trial was an investigator-driven study that was financially supported by Roche (Woerden, The Netherlands), which also supplied study medication. There was no involvement of the study sponsor in the study design, patient recruitment, data collection, analysis and interpretation of the data, or writing of the report.

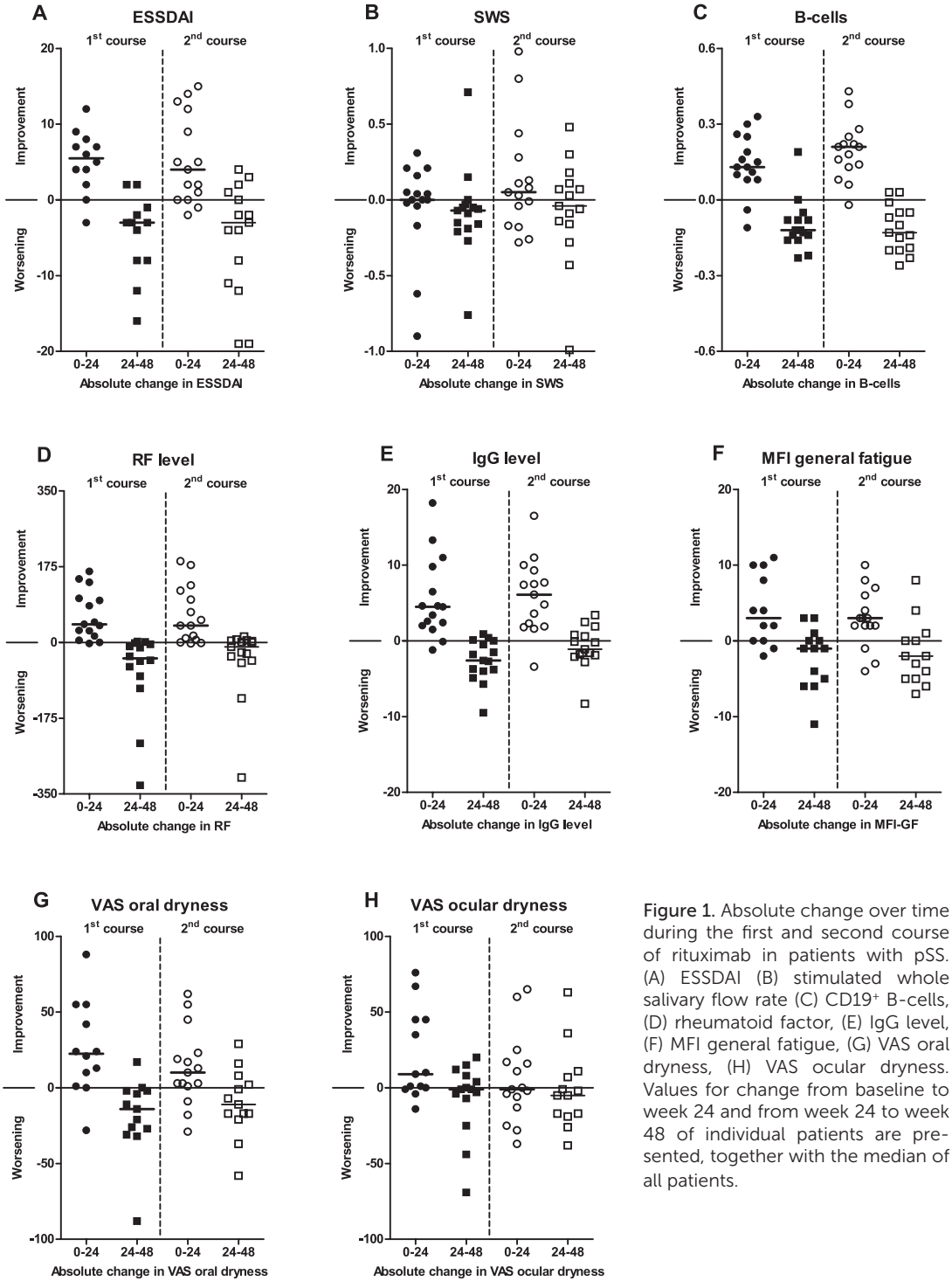

Figure 1. Absolute change over time during the first and second course of rituximab in patients with pSS. (A) ESSDAI (B) stimulated whole salivary flow rate (C) $CD19^{+}$ B-cells, (D) rheumatoid factor, (E) IgG level, (F) MFI general fatigue, (G) VAS oral dryness, (H) VAS ocular dryness. Values for change from baseline to week 24 and from week 24 to week 48 of individual patients are presented, together with the median of all patients.

References

1 Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541-4.

2 Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960-8.

3 Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5.

4 Gottenberg JE, Cinquetti G, Larroche C, et al. Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the Auto Immune and rituximab registry. Ann Rheum Dis 2013;72:1026-31.

5 Meiners PM, Arends S, Brouwer E, et al. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012;71:1297-302.

6 Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

7 Moerman RV, Arends S, Meiners PM, et al. EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomised controlled trial. Ann Rheum Dis 2014;73:472-4.

8 Seror R, Gottenberg JE, Devauchelle-Pensec V, et al. ESSDAI and ESSPRI: EULAR indexes for a complete picture of primary Sjögren's syndrome patients. Arthritis Care Res 2013;65:1358-64.

Chapter 4.3

Treatment of primary Sjögren's syndrome with anti-CD20 therapy (rituximab). A feasible approach or just a starting point?

Petra M Meiners[1], Arjan Vissink[1], Cees GM Kallenberg[2], Frans GM Kroese[2], Hendrika Bootsma[2]

Department of [1]Oral and Maxillofacial Surgery and [2]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, The Netherlands

Expert Opin Biol Ther 2011; 11(10):1381-94.

ABSTRACT

Introduction. *In vitro* and *in vivo* experimental data have pointed to new immunopathogenic mechanisms in primary Sjögren's syndrome (pSS). The availability of targeted treatment modalities has opened new ways to selectively target these mechanistic pathways *in vivo*. Amongst these new treatment modalities, monoclonal antibodies specific for the B-cell surface molecule CD20 have been shown to be the most promising treatment option to date.

Areas covered. A search of the Pubmed, MEDLINE, EMBASE, Cochrane and Ovid databases was performed to review literature on the efficacy and safety profile of anti-CD20 therapy in pSS patients.

Expert opinion. A single course of the chimeric humanised anti-CD20 antibody rituximab was effective in reducing disease activity in pSS patients for about 6 to 9 months. Retreatment of responders resulted in a similar effect to initial treatment. When combined with corticosteroids during infusion, rituximab was shown to be a safe drug to administer. Thus, anti-CD20 therapy can be considered an effective treatment option in pSS patients. However, large randomised controlled trials with anti-CD20 therapy, for example rituximab, are warranted in order to: 1) to assess long-term effects of rituximab treatment, 2) determine which pSS patients will benefit most from anti-CD20 treatment and which (re)treatment schedule should be followed.

INTRODUCTION

Primary Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease primarily characterized by chronic inflammation of the exocrine glands, in particular the salivary and lacrimal glands. This inflammatory process leads to changes in exocrine function. These changes, in their turn, result in a variety of complaints of which a sensation of oral dryness (xerostomia) and a sensation of dry eyes (keratoconjunctivitis sicca) are the most common and most characteristic ones. Also any other organ may be affected in the inflammatory process, leading to extraglandular manifestations, such as arthritis, vasculitis, nephritis and pulmonary involvement, and, importantly, to complaints of restricting chronic fatigue.[1] Furthermore, pSS has a large impact on health-related quality of life (HR-QoL), employment and disability, compared with the general population.[2]

From a pathogenetic point of view, B-lymphocyte hyperactivity is a hallmark of the disease process. B-lymphocyte infiltrations in the salivary glands with development of B-cell follicles containing germinal-center-like-structures are characteristic for pSS.[3] B-lymphocyte hyperactivity in pSS is manifested by the presence of anti-SSA (Ro) and anti-SSB (La) antibodies, elevated levels of rheumatoid factor, type 2 cryoglobulins and hypergammaglobulinemia. Excessive B-cell activity is possibly related to increased production of B-cell activating factor (BAFF) observed in these patients.[4] B-lymphocyte hyperactivity probably also plays an important role in developing mucosa-associated lymphoid tissue (MALT) lymphomas, which occur in 5 to 7.5% of SS patients.[5,6] The classical role of B-cells in the immunopathogenetic process of autoimmune diseases is their role in the production of autoantibodies.[7] However, there is cumulating evidence that B-cells also may exert other important immune functions in the pathogenesis of autoimmune diseases. They can act as antigen presenting cells that drive the autoimmune process as well as that they can serve as an important source of cytokine producing cells, producing immunoregulatory, pro-inflammatory, polarizing and tissue-organizing cytokines.[8]

Treatment of primary Sjögren syndrome

Treatment of SS has been symptomatic for a long time.[9,10] The increasing availability of targeted treatment modalities has created possibilities for intervention in pathogenic pathways involved in the disease. This opened new horizons for treatment, but also gave insight into the pathogenesis of SS.[11] In contrast to rheumatoid arthritis (RA), the role of pro-inflammatory cytokines, in particular tumour necrosis factor α (TNFα), is not very outspoken in SS as demonstrated by the lack of efficacy of TNF-inhibiting therapies.[12] However, B-cell depletion therapy appears to be successful and improves salivary flow and restores, at least partly, the histological organisation of the salivary gland.[13] Furthermore, this therapy results in less sicca complaints, less extraglandular disease, less fatigue and in better HR-QoL. To date, therapy with the anti-CD20 antibody rituximab is

the only effective non-symptomatic therapy known for the treatment of pSS and will be discussed in detail in this paper.

Anti-CD20 therapy

Given the central role of B-cells in the pathogenetic process of pSS, the B-cell surface molecule CD20 has demonstrated a promising target for treatment of rheumatic autoimmune diseases including pSS.[7] CD20 is expressed on the surface of pre-B, transitional B and mature B-lymphocytes, and is lost at the plasma cell stage. CD20 mediates B-cell activation, proliferation and differentiation.[14,15] CD20 may play an important role in the generation of T-cell independent antibody responses.[16]

There are a number of therapeutic monoclonal antibodies currently available targeting CD20. The most frequently applied and studied reagent is rituximab, a chimeric humanised monoclonal anti-CD20 monoclonal antibody. Others are ocrelizumab, a humanised anti-CD20 antibody with enhanced antibody dependent cellular cytotoxicity capabilities compared to rituximab, and ofatumumab, a fully human anti-CD20 antibody. These anti-CD20 antibodies have all been used in the treatment of rheumatic autoimmune diseases.[7] Concerning treatment of pSS, only rituximab (MabThera®, Rituxan®) has been used so far and will be discussed in this paper.

Although rituximab has some intrinsic cytotoxic activity towards B-cells in vitro, it is generally thought that rituximab prevents B-cells from proliferating and induces lysis of B-cells by antibody-dependant cellular cytotoxicity and, to a lesser extent, by complement-dependant cytotoxicity mechanisms.[7] Rituximab is currently used for the treatment of chronic lymphocytic leukaemia,[17] low-grade B-cell lymphomas[17-20] and a variety of autoimmune diseases including RA, systemic lupus erythematosus (SLE), anti-neutrophilic cytoplasmic antibodies associated vasculitis (AAV) and SS. Finally, the off-label use of rituximab includes organ (kidney) transplantation.[7,21]

Regarding their use in autoimmune disease, rituximab was shown, in controlled studies, to be safe and effective in the treatment of RA.[23-27] Furthermore, although open label studies in SLE patients were promising,[28] two randomised controlled trials in patients with moderately to severe SLE failed to show differences in treatment outcome between placebo and rituximab.[29,30] Finally, most uncontrolled studies have reported remissions in 80 to 90% of AAV patients who were treated with rituximab.[31-35] Two randomised controlled trials in AAV showed similar remission rates after rituximab treatment and also showed comparable efficacy and safety profiles for rituximab and cyclophosphamide treatment in patients with AAV.[36,37]

In pSS, initial case reports had shown that treatment with rituximab might have a beneficial effect.[38-40] Thereupon, Pijpe et al[41] showed in an open label study that rituximab indeed might be an effective treatment approach in pSS patients. In this paper we review available data from uncontrolled and controlled trials that studied rituximab in the treatment of pSS.

METHODS

A review of the literature search for the terms 'rituximab', 'anti-CD20', 'biological agent' matched with the term 'Sjögren's syndrome' was performed using PubMed, MEDLINE, EMBASE, Cochrane and Ovid databases. No language restriction was applied. All relevant articles between January 2000 and January 2011 were reviewed. Case reports were excluded.

RESULTS

Open-label studies (for details see table 1)

In a retrospective study including 6 pSS patients, Gottenberg et al[38] reported that rituximab might be beneficial in the treatment of pSS, but the outcome data were not complete in many of the patients.

In the first open-label study (8 patients with early pSS; 7 patients with MALT lymphoma/pSS) reported in the literature, Pijpe et al[41] showed a good clinical response to rituximab. In patients with residual salivary flow, that is a stimulated whole salivary flow rate >0.1 mL/minute at baseline, an increase in stimulated submandibular/sublingual salivary flow was observed. Unstimulated whole salivary flow did not change. Furthermore, improvements in lacrimal function and several subjective measures (e.g., fatigue, HR-QoL) were observed in all patients. As expected, B-cells were fully depleted from the blood in these patients during the first 12 to 24 weeks after initial treatment. Overall, levels of immunoglobulins did, however, not change, although a significant decrease in IgM-rheumatoid factor was seen. These observations may be explained by the fact that IgG secreting plasma cells do not express CD20 and are long-lived,[42] whereas IgM secreting cells (amongst others producing IgM-rheumatoid factor) are generally believed to be short-lived cells.

Meijer et al[43] showed in the extended follow-up of the patients from the study of Pijpe et al[41] that peripheral blood B-cells had returned after 36 weeks (but were still below baseline) and stimulated submandibular/sublingual salivary flow, after initial significant improvement, had declined to just above baseline at 48 weeks. Five of these pSS patients were retreated with rituximab and again, showed a clinical and biological response fully similar to that of the initial treatment effect.

The retrospective multicenter study of Seror et al[44] confirmed the reduction of extraglandular manifestations observed by Pijpe et al,[41] but could not show a beneficial effect of rituximab on sicca symptoms. In these patients, there was no (unstimulated) saliva production at baseline (or was not assessed), indicating that salivary glands were severely affected. Galarza et al[45] reported in their retrospective multicenter study that rituximab improved sicca symptoms and extraglandular manifestations in a subset of pSS patients. Finally, Ramos-Casals et al[46] showed in a study on the off-label use of

Table 1. Trials evaluating the effect of rituximab in pSS patients.

Paper	Design	Follow-up	Number of patients	Dose schedule	Corticosteroid	Primary outcome	Secondary outcomes	Results	Adverse events
Open-label trials									
38	Retrospective multicenter	6-11 months	4 pSS patients 2 pSS/MALT patients	375 mg/m^2/ week for 4 weeks in 5 patients, for 2 weeks in 1 patient	Methylprednisolone in 5 patients	Not well defined	Lacrimal function, extraglandular manifestations, VAS for sicca complaints and fatigue	Improvement of extraglandular manifestations, improvement of sicca complaints and fatigue	Two patients had severe infusion related reactions of which 1 serum sickness
41	Prospective	12 weeks	8 pSS patients with early disease (<4 years)	375 mg/m^2/ week for 4 weeks	Pretreatment with 25 mg prednisolone i.v.	Salivary function	Lacrimal function, serum parameters, VAS for sicca complaints, MFI, SF-36	Increase in salivary function in patients with residual salivary flow (SWS flow rate >0.1 mL/minute at baseline), improvement in lacrimal function, improvement in many domains of MFI and SF-36	Three early pSS patients had severe reactions (serum-sickness like disease), 4 had HACA
41	Prospective	12 weeks	7 pSS/MALT patients	375 mg/m^2/ week for 4 weeks	Pretreatment with 25 mg prednisolone i.v.	Salivary function	Lacrimal function, serum parameters, VAS for sicca complaints, MFI, SF-36, remission rate	No increase in salivary function (all patients had SWS flow rate <0.1 mL/minute at baseline), improvement in lacrimal function, improvement in many domains of MFI and SF-36, complete remission in 3 patients, stable disease in 3 patients and progression in 1 patient	No adverse effects
43*	Prospective	48 weeks (1st course) 48 weeks (2nd course)	7 pSS patients with early disease (<4 years) 5 pSS	375 mg/m^2/ week for 4 weeks 375 mg/m^2/ week for 4 weeks	Pretreatment with 25 mg prednisolone i.v. Pretreatment with 25 mg prednisolone i.v.	Salivary function	Lacrimal function, serum parameters, VAS for sicca complaints, MFI, SF-36	Similar response for (re)treatment as reported by Pijpe et al [2005a], improvements had returned to baseline at 36-48 weeks after (re)treatment	One pSS patient developed serum-sickness like disease

13*	Prospective	12 weeks	5 pSS patients with early disease (<4 years)	375 mg/m^2/week for 4 weeks	Pretreatment with 25 mg prednisolone i.v.	Salivary function	Parotid biopsy at baseline and at 12 weeks	Minor-to-moderate increase of parotid flow rate, decrease of sodium concentration in parotid saliva, reduced glandular inflammation, redifferentiation of lymphoepithelial duct lesion	No adverse effects
48**	Prospective	36 weeks	16 pSS patients with active disease	375 mg/m^2/week for 2 weeks	No concomitant corticosteroids	Safety and biological effects	Salivary function, lacrimal function, serum parameters, tender joint and point counts, VAS scores for sicca complaints, global disease activity, pain and fatigue, SF-36	No changes in salivary flow and lacrimal function, at 12 and 36 weeks, significant improvement of tender point count, VAS scores and SF-36	One pSS patient developed serum-sickness like disease
44	Retrospective multicenter	2-48 months	11 pSS patients 3 pSS/MALT patients 2 pSS/lymphoma patients	375 mg/m^2/week for 4 weeks in 14 patients, for 6 weeks in 1 patient, twice 1 g with an interval of 2 weeks in 1 patient	100 mg methyl-prednisolone	Not well defined	Objective and/or subjective assessment of salivary and lacrimal function, extraglandular manifestations, remission rate	Sicca symptoms were improved in a minority of the patients, extraglandular manifestations improved in most patients, complete remission of lymphoma in 4 of 5 patients, partial remission in 1 of 5 patients	Three patients had adverse effects of which 1 with HACA and serum-sickness like disease
54**	Prospective	10-24 months	15 pSS patients	375 mg/m^2/week for 2 weeks	No concomitant corticosteroids	Not well defined	BAFF levels	Timing of B-cell repopulation is modulated by BAFF. B-cells were absent in salivary tissue for 12 months and had reappeared by 24 months after treatment	Not reported
45	Retrospective multicenter	Up to 24 months	8 pSS patients	375 mg/m^2/week for 4 weeks or twice 1 g with an interval of 2 weeks	Corticosteroids	Not well defined	Extraglandular manifestations and sicca symptoms	Half of the patients responded, both for extraglandular manifestations and for sicca symptoms	Three patients had infusion-related adverse events

Table 1. Continued.

Paper	Design	Follow-up	Number of patients	Dose schedule	Corticosteroid	Primary outcome	Secondary outcomes	Results	Adverse events
Open-label trials									
99**	Prospective	10-24 months	15 pSS	375 mg/m^2/week for 2 weeks	No concomitant corticosteroids	Not well defined	Gene-expression profile	A set of genes might be predictive for the efficacy of rituximab treatment	Not reported
46	Prospective multicenter	12 months	9 pSS patients 6 pSS/MALT or lymphoma patients	375 mg/m^2/week for 4 weeks or twice 1 g with an interval of 2 weeks	Corticosteroids	Not well defined	Complete/partial/no response	67% complete, 20% partial and 13% no response	Two patients had adverse effects
Randomised clinical trials									
50	RCT	12 months	17 pSS patients (9 received placebo)	twice 1 g with an interval of 2 weeks	100 mg methyl-prednisolone i.v.	>20% improvement in VAS for fatigue	Salivary function, lacrimal function, serum parameters, PROFAD, FACIT-F and SF-36	Improvement of fatigue and SF-36 at 6 months, sicca symptoms (objective and subjective) did not improve	One pSS patient developed serum-sickness
51	RCT	48 weeks	30 pSS patients (10 received placebo)	twice 1 g with an interval of 2 weeks	100 mg methyl-prednisolone i.v.	Increased stimulated whole salivary flow rate (at 12 weeks)	Lacrimal function, serum parameters, extraglandular manifestations, VAS for sicca complaints, MFI and SF-36	At 12 weeks improvement of salivary and lacrimal function, serum parameters, extraglandular manifestations, VAS for sicca complaints, MFI and SF-36. By week 48 most improvements had returned to baseline, while the placebo treated patients had worsened	One pSS patient developed serum-sickness like disease

*study (extended follow-up or histopathological analysis of parotid biopsies) in patients that had participated in the study of Pijpe et al.[41]
**patients involved in this study were derived from the study of Devauchelle-Pensec et al.[47]
pSS, primary Sjögren's syndrome; MALT, mucosa-associated lymphoid tissue; VAS, visual analogue scale; MFI, multidimensional fatigue inventory; SF-36, short form 36; SWS, stimulated whole salivary flow rate; HACA, human anti-chimeric antibody; PROFAD, profile of fatigue and discomfort; FACIT-F, functional assessment of chronic illness therapy – fatigue.

rituximab in patients with refractory systemic autoimmune diseases that treatment with rituximab might be favourable in pSS patients with extraglandular involvement.
The results from the open label studies of Pijpe et al[13,41] and Meijer et al[43] showed great resemblance with the results from the open label study of Devauchelle-Pensec et al,[47] in which 16 pSS patients with longstanding disease were treated with rituximab. The latter authors noted a decrease of tender joint and tender point counts, subjective complaints of dryness, arthralgia and fatigue and improved HR-QoL. These improvements were still present 36 weeks after the start of treatment. Patients with shorter disease duration improved more than patients with longer disease duration. Ultrasound and Doppler waveform analysis of the same patients revealed that rituximab treatment was accompanied by, respectively, a significant size reduction of the parotid and submandibular glands and a significant increase in blood inflow responses to salivary stimulation.[48] In these studies B-cells were strongly reduced both in the peripheral blood and labial salivary glands. The focus score (i.e., lymphocytic foci per 4 mm^2) in the labial glands did, however, not change, neither was an increase in unstimulated whole salivary flow rate observed.
Thus, although Pijpe et al,[41] clearly showed a significant improvement of salivary flow in pSS patients treated with rituximab, the study by Devauchelle-Pensec et al[47] could not demonstrate such an effect. Importantly, this improvement of glandular function noted by Pijpe et al[41] was only observed in patients with residual glandular function (stimulated whole salivary flow rate >0.1 mL/minute at baseline). A major difference between the study of Pijpe et al[41] and Devauchelle-Pensec et al[47] is that the first measured stimulated salivary flow too, whereas the latter just measured unstimulated salivary flow. Furthermore the pSS patients in the study of Devauchelle-Pensec et al[47] had much longer disease duration. It is known that pSS patients with longer disease duration are characterized by severely reduced salivary gland secretions.[49] Apparently, a certain level of residual stimulated saliva secretion is a prerequisite when aiming for an increase in salivary flow following rituximab treatment in pSS patients.

Randomised clinical trials (for details see table 1)

Two recent randomised clinical trials (RCT) by Dass et al[50] and Meijer et al,[51] although small in size, have confirmed the efficacy of rituximab in pSS patients. Dass et al[50] included 17 pSS patients (8 patients received rituximab; 9 patients received placebo) in their RCT, and noted a significant decrease in fatigue which persisted for at least 6 months in the rituximab group. Furthermore, Short Form 36 (SF-36) social functioning scores were significantly higher in the rituximab group at 6 months. Unstimulated salivary flow did, however, not change in this group with longstanding pSS (median disease duration of 7.25 years). Levels of salivary flow were not provided this study. As already mentioned in the previous paragraph SS patients with longer disease duration are characterized by severely reduced salivary gland secretions[49] and if salivary flow is too low (or even absent) at baseline, improvement by rituximab treatment is difficult to achieve.

The RCT of Meijer et al[51] included 30 patients (20 patients received rituximab; 10 patients received placebo) with early pSS and showed a significant increase in stimulated whole salivary flow rate (primary endpoint, 12 weeks after start of therapy). In this study also unstimulated salivary flow rate was enhanced. Furthermore, between 12 and 36 weeks after initiation of therapy, improvements compared to baseline were also found for lacrimal function, extraglandular manifestations and subjective parameters (sicca complaints, fatigue and HR-QoL). A decrease in rheumatoid factor, but no change in levels of immunoglobulins was noted up to 36 weeks after treatment.

Together, the data of both the open-label studies and the RCT's provide evidence that rituximab is effective in reducing various disease manifestations of pSS patients, such as sicca complaints, extraglandular manifestations, fatigue and in improving HR-QoL. Currently, there is one larger trial in progress (Tolerance and Efficacy of Rituximab in Sjögren's Disease; TEARS, NCT00740948).[52]

Effect of rituximab on B-cell depletion and repopulation

All clinical studies described above show that rituximab treatment effectively depletes all B-cells in the peripheral blood up to 6 months after initiation of treatment. Studying repopulation of B-cells after rituximab administration showed that the majority of the first B-cells that reappeared had a phenotype of transitional B-cells.[53,54] Recovery of $CD27^+$ memory cells was delayed. T-cells appear to be largely unaffected by rituximab treatment; only a small, but significant increase in number of $CD4^+$ T-cells in the blood was seen in the group of patients with early pSS at week 12 after rituximab.[41] No changes in numbers of regulatory T-cells and effector T-cells and ratios of effector cells to regulatory T-cells were observed.[52] Also, numbers of $CD8^+$ T-cells remained stable.[41]

Despite full depletion of $CD20^+$ B-lymphocytes from the peripheral blood, histopathological analysis of parotid biopsies of 5 early pSS patients obtained 12 weeks after initial treatment still revealed the presence of B-cells.[11] Furthermore in this study, in 4 (out of 5) early pSS patients with a baseline stimulated salivary flow rate of >0.10mL/minute, a strong reduction of the lymphocytic infiltrate was seen. The B:T-cell ratio was decreased, indicating a higher reduction in B-cells than T-cells and there was a (partial) disappearance of germinal-center-like structures.[13] In contrast to these observations, Pers et al[54] observed a complete absence of B-cells in labial salivary gland biopsies up to 1 year after rituximab treatment. Repopulation of these labial salivary glands showed transitional B-cells and memory B-cells as the first B-cells to be identified. Importantly, further analysis of the parotid gland biopsies from the study of Pijpe et al[13] revealed a decrease of intraepithelial lymphocytes in the ducts and redifferentiation of lymphoepithelial duct lesions to normal striated ducts. This recovery of the striated duct compartment was reflected in lower sodium concentrations in parotid saliva, indicating a recovery of the sodium reabsorption capacity of this compartment. The initially observed inflammation-induced increase in cellular proliferation of acinar parenchyma also diminished

after treatment, sometimes even resulting in a normal architecture of acinar structures. These histopathologic findings not only support a role for B-cells in the pathogenesis of pSS, but also offer a possible explanation for improved saliva production after rituximab treatment.

Rituximab in the treatment of lymphoma in pSS

Among patients with SS 5% develop malignant B-cell lymphoma, 48 to 75% of which are of the MALT-type. These lymphomas also express CD20 on their cell surface membrane and are thus a potential target for anti-CD20 therapy.[55-58] Parotid gland enlargement is a common manifestation in pSS patients with a MALT or malignant B-cell lymphoma. The emergence of lymphoma in SS may be heralded by extraglandular manifestations of SS (e.g., palpable purpura, vasculitis, renal involvement, peripheral neuropathy). None of these features are specific for MALT lymphoma in SS, but any of them should raise suspicion, particularly if accompanied by features such as monoclonal gammopathy, reduced levels of complement C4, $CD4^+$ T-lymphocytopenia, a sharp decrease in IgG levels or cryoglobulinemia.[1,58-62]

As already discussed in previous paragraphs, rituximab treatment reduces extraglandular manifestations in pSS. Moreover, Pijpe et al[39,41] showed that rituximab treatment in pSS patients with a MALT lymphoma might result in complete remission of this lymphoma. However, in recent studies it was shown that in SS-MALT patients with initial high SS disease activity rituximab monotherapy is not sufficient for the treatment, because these patients required retreatment due to recurrence of MALT-lymphoma and/or development of SS disease activity.[57,62] In these patients treatment might have to include more intensive immunosuppressive therapy, for instance a combination of rituximab with cyclophosphamide and prednisone (R-CP). This combination therapy is effective in the treatment of both indolent lymphoma and autoimmune disease.[64,65] Pollard et al[58] proposed guidelines for management and treatment of patients with MALT-SS based on their treatment experience in 35 patients with pSS and a lymphoma:

- asymptomatic MALT and low SS disease activity: watchful waiting;
- symptomatic local MALT, no- or low SS disease activity: radiotherapy;
- high SS disease activity and asymptomatic MALT: rituximab only (phase II trial) or immunochemotherapy: R-CP;
- symptomatic MALT and high SS disease activity: R-CP.

Safety of rituximab

Recent data showed that rituximab maintenance therapy significantly increases the risk of both infection and neutropenia in patients with lymphoma or other haematological malignancies.[66] In contrast, rituximab in patients with autoimmune disease does not appear to be associated with an increased infection risk, compared with concurrent control treatments in these patients.[66] The food and drug administration received, however,

reports of 2 SLE patients and 1 RA patient who developed progressive multifocal leukoencephalopathy, an opportunistic infection typically seen in immunocompromised patients. All 3 patients died following rituximab treatment.[67] On the other hand, in RA no cases of other opportunistic infections, tuberculosis, or viral reactivations have been reported after the continuing use of rituximab and there is no evidence of an increased risk of malignancy in these patients.[68] Also in pSS patients, no striking differences in infection rates were seen between placebo- and rituximab-treated patients.[50,51] Furthermore, the rate of infections per 100 patient-years in the RCT of Meijer et al[51] was lower compared with the rate of infections in RA patients[69] treated with rituximab. Although the infection risk seems thus low in patients with autoimmune disease treated with rituximab, it remains to be established whether long-term usage of rituximab will not result in an increased infection risk in these patients.

After treatment with rituximab, both acute infusion reactions (those occurring within 24 hours) and serum sickness (-like) disease can be observed. The most common acute infusion reactions are headache, hypertension, nausea, pruritus, urticaria and flushing. Rituximab infusion reactions are thought to occur largely as a consequence of the degree of B-cell lysis and release of cell contents, rather than as a direct reaction to the agent itself. In contrast, serum sickness (-like) disease, which is an immunocomplex-mediated disease, occurring hours, days, or even weeks after antibody administration, is potentially more problematic.[68] When compared with RA and SLE patients treated with rituximab, patients with pSS develop serum sickness (-like) disease more frequently (6 to 27%).[41,50,70] A therapy-related explanation is that RA and SLE patients often have been treated with intensive immunosuppressive regimens including biological agents before they were exposed to rituximab treatment, whereas pSS patients are far more medication-naïve at the time of rituximab treatment. Another therapy-related explanation for this phenomenon might be that usually higher doses of steroids and/or other immunosuppressive drugs (e.g., methotrexate) besides rituximab have been or are given to RA and SLE patients, whereas most pSS patients received only steroids for 5 days after i.v. administration of rituximab. The higher susceptibility for serum sickness could also be inherent to the disease itself, particularly patients with active, early and progressive forms of pSS are more prone to develop serum sickness.[51] In the study of Devauchelle-Pensec et al[47] no corticosteroid pulse was applied and no serum sickness like disease was reported, but their pSS patients were treated with a lower rituximab dose than in the study of Pijpe et al[41] and Meijer et al[51] as well as that their patients had a longer disease duration (see table 1). Furthermore, hypergammaglobulinaemia is common in pSS patients, which could make these patients prone to the development and deposition of immune complexes and thus to serum sickness(-like) disease.[50] Because of the higher susceptibility for serum sickness, pSS patients may be in need of concomitant administration of corticosteroids when receiving rituximab.[51]

OTHER INTERVENTION THERAPIES IN PSS

Besides rituximab, a variety of other therapies with biologicals aiming to intervene in disease activity or disease progression has been considered or is currently considered to be effective in pSS patients.[11,70] The main findings or perspectives of these therapies are described briefly below and discussed in a broader perspective in the expert opinion section: Is it feasible to combine rituximab with other biologicals?

Tumor-necrosis-factor

TNFα and other pro-inflammatory cytokines are overexpressed in salivary glandular tissue,[71] tears and peripheral blood in patients with pSS.[72,73] As TNFα stimulates the inflammatory response and is also involved in apoptosis of excretory tissue, targeting TNFα in pSS seemed to be justified. In a small open-label pilot study, infliximab, a therapeutically applied chimeric monoclonal IgG1 antibody directed against TNFα was shown to improve subjective and objective assessments of glandular function.[74,75] However, a larger RCT failed to show any effect of infliximab on subjective and objective manifestations of pSS.[12] Also studies using another TNF-blocking agent, etanercept (a fusion protein of the soluble TNF receptor with the Fc part of human IgG1), revealed no effect of inhibiting TNF on a variety of disease parameters in pSS.[76,77]

Interferon-alpha

The type I interferons (IFN) are a group of cytokines released by a wide variety of cells upon interactions with pathogens such as viruses. INFα levels are increased in plasma of patients with pSS.[78,79] Furthermore, sera from pSS patients have high type 1 IFN bioactivity.[80] INFα may stimulate BAFF production by epithelial cells and BAFF seems to be involved in the pathogenetic process (see following paragraph).[81] Thus, interference in pSS with monoclonal antibodies to IFNα seems a rational approach. Clinical trials in SLE and dermatomyositis/polymyositis with monoclonal antibodies to IFNα are underway but clinical trials with these monoclonal antibodies in pSS have not yet been started.
In stead of targeting IFNα, IFNα itself has been used as a therapeutic agent in pSS. Surprisingly, in phase I and phase II studies, it was shown that IFNα might increase salivary and lacrimal function in pSS patients.[82-84] These smaller studies were followed by a phase III RCT on 497 subjects showing that IFNα treatment increased the unstimulated whole salivary flow rate, but not the stimulated whole salivary flow rate and oral dryness.[85] It is currently not clear how the increase in salivary flow following IFNα treatment can be explained.

B-cell activating factor

BAFF, also named B-lymphocyte stimulator (BlyS), is an important member of the TNF family and is involved in B-cell survival and humoral immune responses.[86] BAFF plays a

critical role in B-cell homeostasis. Overexpression of BAFF may result in less stringent selection of transitional B-cells and rescues autoreactive cells from deletion in the periphery,[87-89] collectively leading to higher numbers of mature autoreactive B-cells. Patients with pSS have elevated levels of BAFF in serum, saliva and salivary glands.[90-93] BAFF levels correlate with serum levels of gammaglobulins and IgG.[94] Furthermore, BAFF levels are higher in pSS patients with anti-SSA or anti-SSB antibodies[92,94] and in patients with salivary glands that contain germinal centers.[95] In this context it should be noted here that assessment of BAFF is difficult and is hampered by the fact that soluble BAFF can have multiple forms and variants, which are not always detected by different ELISA's with the same efficiency.[96] Most of the BAFF in salivary glands appears to be produced by infiltrating T- and B-cells and ductal epithelial cells.[91,97] Both virus, type I IFN and (viral) Toll-like receptor ligands are able to stimulate BAFF expression in salivary gland epithelial cells, suggesting that viral infection may be responsible for the increase in BAFF production by ductal epithelial cells.[81,98] A recent study[99] analysed gene expression profiles of labial salivary glands before and after rituximab treatment and related these profiles to the clinical response on rituximab. Interestingly, the latter authors found 2 groups of genes higher expressed in responders than in non-responders. The first group consisted of genes involved in the B-cell signalling pathway and the second group was related to genes involved in the IFN pathway. These data fit in the concept of type-I-IFN-induced BAFF expression in salivary glands of pSS patients. The elevated BAFF levels in pSS patients are subsequently held responsible for B-cell hyperactivation, abnormal distribution of B-cell subsets and autoantibody production seen in these patients.[4]

Rituximab treatment of patients with systemic autoimmune disease (RA, SLE) results in an increase of BAFF protein levels in serum.[100-102] A similar effect of rituximab also was observed in our placebo controlled rituximab trial [Pollard et al, unpublished]. There appears to be an inverse correlation of serum BAFF levels and B-cell numbers in blood. The rise in BAFF levels may be attributable to the absence of B-cells that can bind BAFF to their receptors.[100,102] Since BAFF mRNA levels were higher in peripheral blood mononuclear cells after rituximab treatment[102] loss of B-cells also may result in an upregulation of BAFF mRNA transcription by monocytes and also contribute to the elevated BAFF levels.

Given its role in B-cell homeostasis the higher serum BAFF levels detected after B-cell depletion therapy of patients with systemic autoimmune disease may contribute to sustained autoantibody production by non-deleted (CD20-negative) plasma cells, survival and/or re-emergence of autoreactive B-cells and subsequent clinical relapse.[102] Indeed, in line with this notion, we have recently observed that many of the re-emerging B-cells after rituximab therapy of pSS patients are autoreactive [Abdulahad et al, unpublished]. Because BAFF plays a major role in pSS, it seems logical to target BAFF in pSS patients.

Belimumab, a monoclonal antibody to BAFF, has shown significant benefits for patients with SLE,[103] but data in pSS patients are not yet available. Also other BAFF-blocking

agents such as A-623, atacicept and briobacept have not been used in clinical trials in pSS yet. BAFF is produced as cell-bound cytokine, which is released from the cell surface by proteolytic cleavage. Soluble BAFF can have multiple forms.[104] Not all therapeutic reagents available recognise all these membrane and soluble forms of BAFF with the same affinity, which may result in different outcomes of treatment.[96] Targeting BAFF using 1 of these agents could not only be beneficial for the pSS patients, but may also shed further light on the pathogenic significance of BAFF in pSS.

Co-stimulation

Co-stimulation between antigen-presenting cells and T-cells and between B- and T-cells is an essential step in T-cell-dependent immune responses including autoimmune responses. Salivary gland epithelial cells in pSS have been shown to express both HLA class II and co-stimulatory molecules and may function as antigen-presenting cells in pSS, besides dendritic cells and B-cells.[105] Abatacept, a fusion molecule of IgG-Fc and cytotoxic T-lymphocyte antigen 4 (CTLA-4), modulates CD28-mediated T-cell co-stimulation. This biological is currently used for the treatment of RA and it appears to be safe and effective.[106] A controlled trial with abatacept in pSS has been started, but results of treatment with abatacept in pSS are not yet available.

CONCLUSION

As is obvious from the results of the various studies described, both open-label and RCTs show the efficacy of rituximab in reducing extraglandular manifestations and fatigue, and in increasing HR-QoL. The increase in salivary flow is dependent on the residual function of the glands, which is related to disease duration. Furthermore, rituximab seems to have an acceptable safety profile. However, it has still to be assessed which pSS patients will benefit the most of rituximab treatment as well as which (re)treatment schedule should be followed. Moreover, it has to be assessed whether it is worthwhile to combine rituximab with other biologicals or that other intervention therapies might surpass the beneficial effect of rituximab thus far observed in pSS patients. Finally, despite the acceptable safety profile of rituximab thus far, it remains to be established whether it is also safe to use rituximab on the long-term.

EXPERT OPINION

Is rituximab safe and effective?

Current knowledge of safety and efficacy of rituximab treatment in pSS patients is based on a variety of case reports and open-label trials, while only 2 small RCTs have yet been performed. Although the results of rituximab treatment are promising in most studies,

and its safety profile is acceptable, long-term data are needed before the role of rituximab in the treatment of pSS can be settled; not only with respect to its effect on salivary flow rate and xerostomia, but also with regard to its effect on extraglandular manifestations, fatigue and HR-QoL. Furthermore, most pSS patients treated with rituximab experienced relapse of pSS after reconstitution of B-cells, and not all pSS patients responded to rituximab. Therefore, it is worthwhile to explore the effect of retreatment and to identify predictors of response in large size RCTs with pSS patients.

Which patients will respond and benefit from rituximab treatment?

The answer to this question is hard to address. In the first place, the current knowledge of the efficacy and safety of rituximab in the treatment of pSS patients is, although promising, still limited. Furthermore, until now, consensual outcome measures for treatment evaluation in clinical trials are lacking in pSS. Therefore, there is a great need for a standardised, validated reliable clinical disease activity index facilitating comparison, classification and stratification of patients in clinical trials.[107] Recently, 2 indices have been introduced that might meet this shortcoming, namely a patient-administered questionnaire to assess patient symptoms (European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index; ESSPRI) and a systemic activity index to evaluate systemic complications (EULAR Sjögren's Syndrome Disease Activity Index; ESSDAI).[108] The usefulness of these instruments regarding their reliability, validity and sensitivity to change has to be assessed, before their overall use can be recommended. Perhaps, in the future, response criteria can be formulated based on these indices.

A remarkable finding reported by Pijpe et al[41] was that improvement of sicca complaints mainly occurred in patients with residual salivary function, which is most likely to be present in pSS patients with short disease duration. Patients with early disease also showed more improvements than patients with longer disease duration regarding, amongst others, eye dryness, fatigue and HR-QoL.[41,47] Other manifestations that showed relevant improvement are glandular enlargement[48] and extraglandular manifestations.[38,44,45,47,51] We, therefore, presume that pSS patients with early, active disease with extraglandular manifestations are likely to benefit the most from rituximab treatment.

When to retreat?

The effect of rituximab treatment is transient and treated patients usually experience relapse of the disease. This relapse parallels the return of B-cells in the peripheral blood. Although the duration of treatment effect differed between trials, in all trials a significant effect occurred between 12 to 24 weeks after treatment. Almost all variables had returned to baseline 6 to 9 months after treatment.[41,43,51] Devauchelle-Pensec et al[47] found significant changes from week 12 on, and at week 36 some visual analogue scale (VAS) scores were still improved. In the study of Seror et al[44] clinical relapse was observed 0 to 3 months after the reappearance of peripheral blood B-cells and was associated with

re-increase of B-cell biomarkers (rheumatoid factor, γ-globulins, IgG, ß2-microglobulin). Finally, in the RCT of Dass et al[50] a significant decrease in fatigue persisting for at least 6 months in the rituximab group was observed. The patients in our study[41,43] and most of the patients in the study of Seror et al[44] that were retreated with rituximab responded well and reported a beneficial effect comparable to that of the initial treatment with rituximab.

Based on the above described results, one might consider maintenance treatment. Rituximab infusions (twice 1 g or 500 mg with an interval of 2 weeks) followed by 1 or 2 infusions every 6 to 9 months may be a reasonable approach. Another approach could be retreatment based on return of symptoms. Advantages of maintenance therapy might be a reduction or even arrest of disease progression and improvement of HR-QoL for a long period. The timing of retreatment could also be based on return of symptoms, but retreatment shortly before return of symptoms might even be better.

A threat might be the, so far unknown, long-term side effects of repeated B-cell depletion. Attention has to be paid to, among others, the possibility of development of humoral immunodeficienty related to repeated treatment.[109] Therefore, the best approach to and timing of maintenance treatment has to be studied in future trials.

Can efficacy be increased?

Future, larger trials hopefully will provide data how to select responders beforehand, as well as how to determine the optimal schedule of retreatment. This knowledge will probably increase the efficacy of rituximab in the treatment of pSS. Furthermore, in our experience, rituximab monotherapy was not sufficient in some pSS patients with severe extraglandular manifestations, such as vasculitis, nephritis or polyneuropathy. Treatment in these patients should probably include more intensive immunosuppressive therapy, for instance a combination of rituximab with long-term steroids or a combination of rituximab with cyclophosphamide and prednisone.[58]

Is it beneficial to combine rituximab with other biologicals?

The authors would like to emphasize that thus far, there is a lack of sufficient long-term data to allow statements on efficacy and safety of rituximab 'monotherapy' in pSS to be definitely made. Large RCTs with rituximab in pSS patients with long-term follow-up are needed, before combining rituximab with other biologicals can even be considered. However, theoretically, combining rituximab with other biologicals may be beneficial, for instance, a combination therapy that targets CD20 (rituximab) and BAFF. B-cells seem to play a major role in orchestrating the pathological immune response in pSS. Depleting B-cells offers a unique possibility to study the immunopathogenesis of pSS. BAFF appears a strong stimulant for B-cell activation and proliferation and for B-cell survival in pSS. Pers et al[54] showed that higher baseline serum levels of BAFF in pSS patients resulted in a shorter duration of B-cell depletion by rituximab. This may indicate

that there is a role of BAFF in the repopulation of B-cells after rituximab treatment. A combination therapy that targets CD20 (rituximab) and BAFF may therefore delay B-cell repopulation (with auto-reactive cells) and re-emergence of clinical symptoms.
Also targeting co-stimulation (e.g., with abatacept) at some time point after rituximab treatment, but before the reappearance of B-cells in the blood, may prevent the activation of autoreactive B-cells that either escaped rituximab treatment or were newly generated. Also this combination might therefore be a beneficial approach.

Article highlights.

- Since pSS is a common systemic autoimmune disease (prevalence 0.5 to 1.5%) with a major impact on patients' daily functioning and HR-QoL, there is an unmet need for development of adequate treatment modalities to reduce SS related complaints, to increase HR-QoL and to intervene in the progression and disease activity of pSS.
- Both open-label trials and RCTs showed the efficacy of rituximab in reducing, amongst others, extraglandular manifestations and fatigue, and in increasing HR-QoL, whereas the increase in salivary flow is dependent on the residual function of the glands which is related to disease duration.
- Patients with early disease showed more improvements than pSS patients with longer disease duration regarding, amongst others, oral and eye dryness, fatigue and HR-QoL.
- Histopathological findings underline the efficacy of B-cell depletion and indicate the potential for regeneration of glandular tissue in pSS.
- The results of the various studies are difficult to compare due to a variety in methods used to assess the effect of rituximab on pSS disease activity and progression. Development and wide use of disease activity and disease damage indices may facilitate the evaluation of new treatment options in pSS. In this respect, the recently developed ESSDAI and ESSPRI might be promising.
- Large size RCTs with rituximab are warranted, to assess long-term effects of rituximab treatment, to assess which pSS patients will benefit the most from rituximab treatment, to assess which (re)treatment schedule should be followed, and whether it is worthwhile to combine rituximab with other biologicals.

Drug summary.

Drug name	Rituximab
Indication	Non-Hodgkin's lymphoma Chronic lymphocytic leukaemia Rheumatoid arthritis Anti-neutrophilic-cytoplasmic-antibodies-associated vasculitis (pending)
Phase	IIa in primary Sjögren's syndrome (pre-registration)
Pharmacological description	Monoclonal antibody, Anti-CD20
Route of administration	Intravenous
Pivotal trial(s)	[50,51]

References

1 Fox RI. Sjögren's syndrome. Lancet 2005;366:321-31.

2 Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology 2009;48:1077-82.

3 Hansen A, Lipsky PE, Dorner T. New concepts in the pathogenesis of Sjögren syndrome: many questions, fewer answers. Curr Opin Rheumatol 2003;15:563-70.

4 Varin MM, Le Pottier L, Youinou P, et al. B-cell tolerance breakdown in Sjögren's syndrome: focus on BAFF. Autoimmun Rev 2010;9:604-8.

5 Baimpa E, Dahabreh IJ, Voulgarelis M, et al. Hematologic manifestations and predictors of lymphoma development in primary Sjögren syndrome: clinical and pathophysiologic aspects. Medicine 2009;88:284-93.

6 Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978;89:888-92.

7 Engel P, Gómez-Puerta JA, Ramos-Casals M, et al. Therapeutic targeting of B cells for rheumatic autoimmune diseases. Pharmacol Rev 2011;63:127-56.

8 Anolik JH, Looney RJ, Lund FE, et al. Insights into the heterogeneity of human B cells: diverse functions, roles in autoimmunity, and use as therapeutic targets. Immunol Res 2009;45:144-58.

9 Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjögren syndrome: a systematic review. JAMA 2010;304:452-60.

10 Vissink A, Kallenberg CG, Bootsma H. Treatment approaches in primary Sjögren syndrome. JAMA 2010;304:2015-6.

11 Kallenberg CGM, Vissink A, Kroese FGM, et al. What have we learned from clinical trials in primary Sjögren's syndrome about pathogenesis? Arthritis Res Ther 2011;13:205.

12 Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). Arthritis Rheum 2004;50:1270-6.

13 Pijpe J, Meijer JM, Bootsma H, et al. Clinical and histologic evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjögren's syndrome. Arthritis Rheum 2009;60:3251-6.

14 Tedder TF, Forsgren A, Boyd AW, et al. Antibodies reactive with the B1 molecule inhibit cell cycle progression but not activation of human B lymphocytes. Eur J Immunol 1986;16:881-7.

15 Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface molecule B1 is functionally linked with B cell activation and differentiation. J Immunol 1985;135:973-9.

16 Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest 2010;120:214-22.

17 Keating GM. Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma. Drugs 2010;70:1445-76.

18 Goy A, Kahl B. Mantle cell lymphoma: the promise of new treatment options. Crit Rev Oncol Hematol 2010.

19 McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-33.

20 Saini KS, Azim HA, Jr., Cocorocchio E, et al. Rituximab in Hodgkin lymphoma: is the target always a hit? Cancer Treat Rev 2010.

21 Vo AA, Lukovsky M, Toyoda M, et al. Rituximab and intravenous immune globulin for desensitization during renal transplantation. N Engl J Med 2008;359:242-51.

22 Mease PJ, Cohen S, Gaylis NB, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. J Rheumatol 2010;37:917-27.

23 Tak PP, Rigby WF, Rubbert-Roth A, et al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE

trial. Ann Rheum Dis 2011;70:39-46.

24 Finckh A, Ciurea A, Brulhart L, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56:1417-23.

25 Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54:2793-806.

26 Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum 2006;54:1390-400.

27 Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004;350:2572-81.

28 Looney RJ, Anolik JH, Campbell D, et al. B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. Arthritis Rheum 2004;50:2580-9.

29 Furie RA, Looney RJ, Rovin B et al. Efficacy and safety of rituximab in subjects with active proliferative lupus nephritis (LN): results from the randomized, double-blind phase III LUNAR study (abstract no. 1149). American College of Rheumatology National Meeting 2009.

30 Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum 2010;62:222-33.

31 Lovric S, Erdbruegger U, Kumpers P, et al. Rituximab as rescue therapy in anti-neutrophil cytoplasmic antibody-associated vasculitis: a single-centre experience with 15 patients. Nephrol Dial Transplant 2009;24:179-85.

32 Brihaye B, Aouba A, Pagnoux C, et al. Adjunction of rituximab to steroids and immunosuppressants for refractory/relapsing Wegener's granulomatosis: a study on 8 patients. Clin Exp Rheumatol 2007;25:S23-S27.

33 Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. J Intern Med 2005;257:540-8.

34 Stasi R, Stipa E, Del Poeta G, et al. Long-term observation of patients with anti-neutrophil cytoplasmic antibody-associated vasculitis treated with rituximab. Rheumatology (Oxford) 2006;45:1432-6.

35 Keogh KA, Ytterberg SR, Fervenza FC, et al. Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006;173:180-7.

36 Jones RB, Tervaert JW, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211-20.

37 Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221-32.

38 Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis 2005;64:913-20.

39 Pijpe J, van Imhoff GW, Vissink A, et al. Changes in salivary gland immunohistology and function after rituximab monotherapy in a patient with Sjögren's syndrome and associated MALT lymphoma. Ann Rheum Dis 2005;64:958-60.

40 Somer BG, Tsai DE, Downs L, et al. Improvement in Sjögren's syndrome following therapy with rituximab for marginal zone lymphoma. Arthritis Rheum 2003;49:394-8.

41 Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005;52:2740-50.

42 Hiepe F, Dörner T, Hauser AE, et al. Long-lived autoreactive plasma cells drive persistent autoimmune inflammation. Nat Rev Rheumatol.

2011;7:170-8.

43 Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5.

44 Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis 2007;66:351-7.

45 Galarza C, Valencia D, Tobon GJ, et al. Should rituximab be considered as the first-choice treatment for severe autoimmune rheumatic diseases? Clin Rev Allergy Immunol 2008;34:124-8.

46 Ramos-Casals M, Garcia-Hernandez FJ, de Ramon E, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol 2010;28:468-76.

47 Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007;57:310-7.

48 Jousse-Joulin S, Devauchelle-Pensec V, Morvan J, et al. Ultrasound assessment of salivary glands in patients with primary Sjögren's syndrome treated with rituximab: quantitative and Doppler waveform analysis. Biologics 2007;1:311-9.

49 Pijpe J, Kalk WW, Bootsma H, et al. Progression of salivary gland dysfunction in patients with Sjögren's syndrome. Ann Rheum Dis 2007;66:107-12.

50 Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren's syndrome with rituximab: results of a randomised, double-blind, placebo controlled pilot study. Ann Rheum Dis 2008.

51 Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960-8.

52 University hospital, Brest. Tolerance and Efficacy of Rituximab in Sjogren's Disease. ClinicalTrials.gov NCT00740948 Available from http://clinicaltrials.gov/ct2/show/ NCT00740948.

53 Abdulahad WH, Meijer JM, Kroese FG, et al. B-cell reconstitution and T-helper-cell balance after rituximab treatment of active primary Sjögren's syndrome. Arthritis Rheum 2011;63:1116-23.

54 Pers JO, Devauchelle V, Daridon C, et al. BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjögren's syndrome. Arthritis Rheum 2007;56:1464-77.

55 Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978;89:888-92.

56 Tzioufas AG, Boumba DS, Skopouli FN, et al. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjögren's syndrome. Arthritis Rheum 1996;39:767-72.

57 Voulgarelis M, Dafni UG, Isenberg DA, et al. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. Arthritis Rheum 1999;42:1765-72.

58 Pollard RP, Pijpe J, Bootsma H, et al. Treatment of MALT lymphoma in Sjögren's syndrome: a retrospective clinical study. J Rheumatol 2011;38:2198-208.

59 Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjögren's syndrome. Arthritis Rheum 2002;46:741-7.

60 Ramos-Casals M, Brito-Zeron P, Yague J, et al. Hypocomplementaemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2005;44:89-94.

61 Theander E, Henriksson G, Ljungberg O, et al. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006;65:796-803.

62 Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjögren's

syndrome: a prospective cohort study. Arthritis Rheum 2004;50:1262-9.

63 Quartuccio L, Fabris M, Salvin S, et al. Controversies on rituximab therapy in Sjögren syndrome-associated lymphoproliferation. Int J Rheumatol. 2009;2009:424935.

64 Chambers SA, Isenberg D. Anti-B cell therapy (rituximab) in the treatment of autoimmune diseases. Lupus 2005;14:210-4.

65 Czuczman MS, Grillo-Lopez AJ, White CA, et al. Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol 1999;17:268-76.

66 Kelesidis T, Daikos G, Boumpas D, et al. Does rituximab increase the incidence of infectious complications? A narrative review. Int J Infect Dis 2011;15:e2-e16.

67 Life-threatening brain infection in patients with systemic lupus erythemantosus after Rituxan (rituximab) treatment. FDA Public Health Advisory: US Food and Drug Administration, 2006. Available from http://www.fda.gov (Last accessed 19 July 2011).

68 Fleischmann RM. Safety of biologic therapy in rheumatoid arthritis and other autoimmune diseases: focus on rituximab. Semin Arthritis Rheum 2009;38:265-80.

69 Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum 2007;56:3896-908.

70 Meijer JM, Pijpe J, Bootsma H, et al. The future of biologic agents in the treatment of Sjogren's syndrome. Clin Rev Allergy Immunol 2007;32:292-7.

71 Koski H, Janin A, Humphreys-Beher MG, et al. Tumor necrosis factor-alpha and receptors for it in labial salivary glands in Sjögren's syndrome. Clin Exp Rheumatol 2001;19:131-7.

72 Baturone R, Soto MJ, Marquez M, et al. Health-related quality of life in patients with primary Sjögren's syndrome: relationship with serum levels of proinflammatory cytokines. Scand J Rheumatol 2009;38:386-9.

73 Yoon KC, Jeong IY, Park YG, et al. Interleukin-6 and tumor necrosis factor-alpha levels in tears of patients with dry eye syndrome. Cornea 2007;26:431-7.

74 Steinfeld SD, Demols P, Salmon I, et al. Infliximab in patients with primary Sjögren's syndrome: a pilot study. Arthritis Rheum 2001;44:2371-5.

75 Steinfeld SD, Demols P, Appelboom T. Infliximab in primary Sjögren's syndrome: one-year followup. Arthritis Rheum 2002;46:3301-3.

76 Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjögren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240-5.

77 Zandbelt MM, de Wilde P, van Damme P, et al. Etanercept in the treatment of patients with primary Sjögren's syndrome: a pilot study. J Rheumatol 2004;31:96-101.

78 Bave U, Nordmark G, Lovgren T, et al. Activation of the type I interferon system in primary Sjögren's syndrome: a possible etiopathogenic mechanism. Arthritis Rheum 2005;52:1185-95.

79 Zheng L, Zhang Z, Yu C, et al. Association between IFN-alpha and primary Sjögren's syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:e12-e18.

80 Wildenberg ME, Helden-Meeuwsen CG, van de Merwe JP, et al. Systemic increase in type I interferon activity in Sjögren's syndrome: a putative role for plasmacytoid dendritic cells. Eur J Immunol 2008;38:2024-33.

81 Ittah M, Miceli-Richard C, Eric Gottenberg J, et al. B cell-activating factor of the tumor necrosis factor family (BAFF) is expressed under stimulation by interferon in salivary gland epithelial cells in primary Sjögren's syndrome. Arthritis Res Ther 2006;8:R51.

82 Ferraccioli GF, Salaffi F, De Vita S, et al. Interferon alpha-2 (IFN alpha 2) increases lacrimal and salivary function in Sjögren's syndrome patients. Preliminary results of an open pilot trial versus OH-chloroquine. Clin Exp Rheumatol 1996;14:367-71.

83 Shiozawa S, Morimoto I, Tanaka Y, et al. A preliminary study on the interferon-alpha treat-

ment for xerostomia of Sjögren's syndrome. Br J Rheumatol 1993;32:52-4.

84 Ship JA, Fox PC, Michalek JE, et al. Treatment of primary Sjögren's syndrome with low-dose natural human interferon-alpha administered by the oral mucosal route: a phase II clinical trial. IFN Protocol Study Group. J Interferon Cytokine Res 1999;19:943-51.

85 Smith JK, Siddiqui AA, Modica LA, et al. Interferon-alpha upregulates gene expression of aquaporin-5 in human parotid glands. J Interferon Cytokine Res 1999;19:929-35.

86 Moisini I, Davidson A. BAFF: a local and systemic target in autoimmune diseases. Clin Exp Immunol 2009;158:155-63.

87 Thien M, Phan TG, Gardam S, et al. Excess BAFF rescues self-reactive B cells from peripheral deletion and allows them to enter forbidden follicular and marginal zone niches. Immunity 2004;20:785-98.

88 Ota M, Duong BH, Torkamani A, et al. Regulation of the B cell receptor repertoire and self-reactivity by BAFF. J Immunol 2010;185:4128-36.

89 Lesley R, Xu Y, Kalled SL, et al. Reduced competitiveness of autoantigen-engaged B cells due to increased dependence on BAFF. Immunity 2004;20:441-53.

90 Groom J, Kalled SL, Cutler AH, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjögren's syndrome. J Clin Invest 2002;109:59-68.

91 Lavie F, Miceli-Richard C, Quillard J, et al. Expression of BAFF (BLyS) in T cells infiltrating labial salivary glands from patients with Sjögren's syndrome. J Pathol 2004;202:496-502.

92 Pers JO, Daridon C, Devauchelle V, et al. BAFF overexpression is associated with autoantibody production in autoimmune diseases. Ann N Y Acad Sci 2005;1050:34-9.

93 Pers JO, d'Arbonneau F, Devauchelle-Pensec V, et al. Is periodontal disease mediated by salivary BAFF in Sjögren's syndrome? Arthritis Rheum 2005;52:2411-4.

94 Mariette X, Roux S, Zhang J, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjögren's syndrome. Ann Rheum Dis 2003;62:168-71.

95 Szodoray P, Alex P, Jonsson MV, et al. Distinct profiles of Sjögren's syndrome patients with ectopic salivary gland germinal centers revealed by serum cytokines and BAFF. Clin Immunol 2005;117:168-76.

96 Le Pottier L, Bendaoud B, Renaudineau Y, et al. New Elisa for B cell-activating factor. Clin Chem 2009;55:1843-51.

97 Daridon C, Devauchelle V, Hutin P, et al. Aberrant expression of BAFF by B lymphocytes infiltrating the salivary glands of patients with primary Sjögren's syndrome. Arthritis Rheum 2007;56:1134-44.

98 Ittah M, Miceli-Richard C, Gottenberg JE, et al. Viruses induce high expression of BAFF by salivary gland epithelial cells through TLR- and type-I IFN-dependent and -independent pathways. Eur J Immunol 2008;38:1058-64.

99 Devauchelle-Pensec V, Cagnard N, Pers JO, et al. Gene expression profile in the salivary glands of primary Sjögren's syndrome patients before and after treatment with rituximab. Arthritis Rheum 2010;62:2262-71.

100 Cambridge G, Stohl W, Leandro MJ, et al. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis Rheum 2006;54:723-32.

101 Cambridge G, Isenberg DA, Edwards JC, et al. B cell depletion therapy in systemic lupus erythematosus: relationships among serum B lymphocyte stimulator levels, autoantibody profile and clinical response. Ann Rheum Dis 2008;67:1011-6.

102 Lavie F, Miceli-Richard C, Ittah M, et al. Increase of B cell-activating factor of the TNF family (BAFF) after rituximab treatment: insights into a new regulating system of BAFF production. Ann Rheum Dis 2007;66:700-3.

103 Wiglesworth AK, Ennis KM, Kockler DR. Belimumab: a BLyS-specific inhibitor for systemic lupus erythematosus. Ann Pharmacother 2010;44:1955-61.

104 Mackay F, Schneider P. Cracking the BAFF code. Nature Rev Immunol 2009;9:491-502.

105 Routsias JG, Tzioufas AG. Autoimmune response and target autoantigens in Sjögren's syndrome. Eur J Clin Invest 2010;40:1026-36.

106 Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 2008;67:547-54.

107 Vissink A, Bootsma H, Spijkervet FKL, et al. Current and future challenges in primary Sjögren's syndrome., Curr Pharm Biotechnol 2012;13:2026-45.

108 Seror R, Ravaud P, Bowman S, et al. EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): Development of a consensus systemic disease activity index in primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

109 Popa C, Leandro MJ, Cambridge G, et al. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. Rheumatology (Oxford) 2007;46:626-30.

Chapter 5

Evaluation of disease activity in primary Sjögren's syndrome

Chapter 5.1

Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab

Petra M Meiners[1], Suzanne Arends[2], Liesbeth Brouwer[2], Fred KL Spijkervet[1], Arjan Vissink[1], Hendrika Bootsma[2]

Departments of [1]Oral and Maxillofacial Surgery and [2]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, The Netherlands

Ann Rheum Dis. 2012;71:1297-302

ABSTRACT

Objective. To evaluate the responsiveness of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) in patients with primary Sjögren's syndrome (pSS) treated with rituximab.

Methods. Twenty-eight patients with pSS treated with rituximab (1000 mg) infusions on days 1 and 15 were included in the study. Data were collected prospectively at baseline and 16, 24, 36, 48 and 60 weeks after treatment. Internal responsiveness was assessed using standardised response means (SRM) and effect sizes (ES). SRM and ES <0.5, 0.5-0.8 and >0.8 were interpreted as small, moderate and large, respectively. External responsiveness was assessed using Spearman correlation coefficients.

Results. Median (range) ESSPRI and ESSDAI scores at baseline were 6.7 (0.3-9.0) and 8 (2-18), respectively. Both indices improved significantly after treatment. SRM and ES for ESSPRI and ESSDAI were ≥0.8 at week 16 and decreased afterwards, and were larger for ESSDAI than for ESSPRI. SRM and ES values for patient's and physician's global disease activity (GDA) and rheumatoid factor broadly followed the pattern of those of ESSPRI and ESSDAI. SRM and ES for stimulated whole salivary flow rates were small at all time points. At baseline and for most change scores, moderate to good correlations were found between ESSPRI and patient's GDA and between ESSDAI and physician's GDA. Poor association was found between ESSPRI and ESSDAI.

Conclusion. ESSPRI and ESSDAI are sensitive measures of change in disease activity after therapeutic intervention, which supports the usefulness of these indices for future clinical trials in patients with pSS. The responsiveness of ESSDAI was greater than that of ESSPRI.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disease primarily characterized by chronic inflammation of the exocrine glands.[1] The salivary and lacrimal glands are most commonly affected, resulting in dry mouth and eyes. These sicca symptoms may be accompanied by extraglandular manifestations that may involve almost any organ such as the joints, lungs or skin (vasculitis). Moreover, almost all patients with SS have restricting chronic fatigue.

Since many patients with SS have reduced health-related quality of life and are restricted in their social and work related activities, there is a clear need for development of adequate treatment modalities to reduce SS-related symptoms and to halt progression of the disease.[2-4] To date, rituximab, a chimeric murine/human anti-CD20 monoclonal antibody, is the only effective non-symptomatic therapy known for primary SS (pSS). Data from both open-label trials and randomised clinical trials provide evidence that rituximab is effective in reducing glandular and systemic disease manifestations of pSS.[3-12]

The heterogeneous nature of pSS, as well as its variable course, has made it difficult to quantify the extent and severity of the disease in individual patients. Two indices have recently been introduced that might meet this shortcoming, a patient-administered questionnaire to assess patient symptoms (European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient Reported Index, ESSPRI) and a systemic activity index to evaluate systemic complications (EULAR Sjögren's Syndrome Disease Activity Index, ESSDAI).[13,14] The usefulness of instruments designed to measure change over time or after therapeutic intervention is dependent on their validity and reliability and also on their potential to detect clinically relevant changes.[15,16] Seror and collegues[17] retrospectively investigated the sensitivity to change of ESSDAI over time in 96 patient profiles abstracted from the medical charts of patients with pSS. These authors used the assessment of whether the patient's condition changed or remained stable as an external anchor. Interestingly, the responsiveness of ESSDAI was found to be large, and it seemed to detect change over time more accurately than other known indices.[17] Prospective data on the responsiveness of ESSDAI after therapeutic intervention in pSS patients are currently lacking. Furthermore, no data on responsiveness of ESSPRI are yet available. The aim of this study was therefore to evaluate responsiveness of ESSPRI and ESSDAI in patients with pSS who were treated with rituximab.

PATIENTS AND METHODS

Study design

A prospective, single-center study was performed.

Patients

All 28 patients were aged 18 years and fulfilled the revised American-European Consensus Group criteria for pSS.[18] Patients were enrolled as part of a long term follow-up study of (re)treatment with rituximab and were treated with rituximab (1000 mg) infusions at days 1 and 15 as first (n=8), second (n=15), third (n=3) or fourth (n=2) course of rituximab treatment. (Re)treatment was started when B-cell levels increased, rheumatoid factor (RF) levels increased, salivary flow decreased, subjective symptoms (sicca, fatigue) increased and/or extraglandular manifestations reappeared. Patients were evaluated at baseline and 16, 24, 36, 48 and 60 weeks after rituximab treatment.

Disease activity assessments

Disease activity was assessed using ESSPRI, ESSDAI, patient's and physician's global disease activity (GDA; on a 10 cm visual analogue scale), RF level and stimulated whole salivary flow rate (SWS). ESSPRI is a patient-administered questionnaire to assess patient symptoms, whereas ESSDAI is a physician-administered systemic activity index to evaluate systemic complications.[14,17] A description of ESSPRI and ESSDAI is given table 1. ESSDAI and physician's GDA were assessed by 2 experienced rheumatologists. The RF level was measured by nephelometry. SWS was collected in a standardised manner at a fixed time of the day.[19,20] Flow rates were calculated according to the methods described by Burlage et al[21] and Kalk et al.[22,23]

Statistical analysis

Generalised estimating equations were used to analyse disease activity assessments over time within subjects. Simple contrasts were used to compare follow-up visits with baseline.

Internal responsiveness was defined as described by Husted et al,[24] namely, the ability of a measure to change over a particular prespecified time frame. Internal responsiveness was assessed for all visits (compared with baseline) and for all disease activity assessments using standardised response mean (SRM) and effect size (ES). SRM was calculated as mean change in score between 2 visits divided by the SD of the change in score, whereas ES was calculated as mean change in score between 2 visits divided by the SD of the baseline score.[24] SRM and ES <0.5 were interpreted as small, 0.5-0.8 as moderate and >0.8 as large.[17,25] As indicated by Seror et al,[17] the larger the SRM or ES for improved or worsened disease activity, the greater the responsiveness of the measure investigated. Furthermore, a SRM or an ES closer to zero when disease activity is unchanged indicates that the assessment of stability is more accurate.

The effect of rituximab is transient and treated patients usually experience relapse of pSS. This relapse parallels with return of B-cells in the peripheral blood. Although the duration of treatment effect differed between trials, it is usually seen from 12 weeks up to 24 or 36 weeks after treatment.[12] We therefore expect large SRM and ES for ESSPRI

Table 1. Description of ESSPRI[13] and ESSDAI.[14]

ESSPRI		
Domain	**Activity level**	**Final score**
Pain	0-10	Final score = mean of all 3 domain scores
Fatigue	0-10	
Dryness	0-10	
		Range of theoretical values 0-10
ESSDAI		
Domain (weight)	**Activity level**	**Final score**
1. Constitutional (3)	No (0), low (1), moderate (2)	Final score = sum of the score of each domain; score of each domain = activity level x weight of the domain
2. Lymphadenopathy (4)	No (0), low (1), moderate (2), high (3)	
3. Glandular (2)	No (0), low (1), moderate (2)	
4. Articular (2)	No (0), low (1), moderate (2), high (3)	
5. Cutaneous (3)	No (0), low (1), moderate (2), high (3)	
6. Pulmonary (5)	No (0), low (1), moderate (2), high (3)	Range of theoretical values 0-123
7. Renal (5)	No (0), low (1), moderate (2), high (3)	
8. Muscular (6)	No (0), low (1), moderate (2), high (3)	
9. PNS (5)	No (0), low (1), moderate (2), high (3)	Range of observed values 0-49
10. CNS (5)	No (0), low (1), high (3)	
11. Haematological (2)	No (0), low (1), moderate (2), high (3)	
12. Biological (1)	No (0), low (1), moderate (2)	

ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; PNS, peripheral nervous system; CNS, central nervous system.

and ESSDAI within this time frame and smaller values afterwards. SRM and ES were calculated between week 16 (supposed best effect of rituximab) and week 60, to evaluate the ability of flare detection of disease activity measures.

External responsiveness reflects the extent to which changes in a measure over a specified time frame relate to corresponding changes in a reference measure of health status.[24] External responsiveness was assessed by relating scores of ESSPRI and ESSDAI to each other and to patient's GDA, physician's GDA, RF level and SWS using Spearman's correlation coefficients (ρ). Correlations <0.3 were interpreted as poor association, 0.3-0.6 as moderate association, 0.6-0.8 as good association and >0.8 as excellent association. It was hypothesized a priori that the correlations between ESSPRI and patient's GDA and between ESSDAI and physician's GDA would be moderate to good, indicating that they assess related but slightly different outcome constructs. Furthermore, it was hypothesized that RF and SWS would have no more than moderate correlation with the ESSPRI and ESSDAI, since these measures enfold only a small proportion of the clinical signs of pSS. Statistical analysis was performed with PASW Statistics 18 (SPSS, Chicago, Illinois, USA). p Values <0.05 were considered statistically significant.

Table 2. Baseline characteristics of the primary Sjögren's syndrome study population (n=28).

Variable	Mean±SD or n (%)	Median (range)
Age (years)	43±14	40 (18–70)
Female gender, n (%)	27 (96)	
Disease duration (months)	80±48	64 (14–183)
IgG (g/L)	22.5±7.4	21.3 (12.8–41.5)
RF (kIU/L)	143±164	90 (7–783)
Anti-Ro / SSA positive (n, %)	28 (100)	
Anti-La / SSB positive (n, %)	20 (71)	
SWS (mL/minute)	0.42±0.37	0.31 (0.02–1.47)
Rituximab course number (n, %)		
1st	8 (29)	
2nd	15 (54)	
3rd	3 (11)	
4th	2 (7)	
ESSPRI	6.3±2.2	6.7 (0.3-9.0)
ESSDAI	8±5	8 (2–18)
Constitutional domain, n (%)*	12 (43)	
Lymphadenopathy domain, n (%)*	0 (0)	
Glandular domain, n (%)*	17 (61)	
Articular domain, n (%)*	8 (29)	
Cutaneous domain, n (%)*	4 (14)	
Pulmonary domain, n (%)*	3 (11)	
Renal domain, n (%)*	1 (4)	
Muscular domain, n (%)*	0 (0)	
PNS domain, n (%)*	2 (7)	
CNS domain, n (%)*	0 (0)	
Haematological domain, n (%)*	11 (39)	
Biological domain, n (%)*	24 (86)	
Patient's GDA	58±22	60 (15–93)
Physician's GDA	53±16	55 (20–80)

Values are presented as mean±SD unless otherwise indicated.
*Number (%) of patients having any degree of activity per ESSDAI domain (score of at least 1).
RF, rheumatoid factor; SWS, stimulated whole salivary flow rate; ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; PNS, peripheral nervous system; CNS, central nervous system; GDA, global disease activity assessment.

Table 3. Disease activity in patients with primary Sjögren's syndrome treated with rituximab.

Outcome	Baseline	Week 16	p Value*	Week 24	p Value*	Week 36	p Value*	Week 48	p Value*	Week 60	p Value*
ESSPRI	6.3±2.2 (6.7)	4.6±2.0 (5.3)	0.000	5.3±2.0 (5.3)	0.001	5.3±2.0 (5.3)	0.007	5.8±1.9 (6.3)	0.068	5.6±2.2 (5.7)	0.043
ESSDAI	8±5 (8)	3±3 (2)	0.000	3±3 (2)	0.000	3±3 (2)	0.000	5±7 (4)	0.064	8±6 (5)	0.662
Patient's GDA	58±22 (60)	31±25 (26)	0.000	38±24 (37)	0.000	30±21 (25)	0.000	35±22 (32)	0.000	43±25 (46)	0.010
Physician's GDA	53±16 (55)	15±9 (11)	0.000	10±7 (10)	0.000	14±11 (10)	0.000	24±15 (20)	0.000	36±20 (40)	0.000
RF	143±164 (90)	65±75 (41)	0.000	65±79 (38)	0.000	96±150 (41)	0.000	130±195 (59)	0.275	159±251 (66)	0.587
SWS	0.42±0.37 (0.31)	0.46±0.48 (0.29)	0.272	0.49±0.47 (0.32)	0.256	0.45±0.49 (0.27)	0.692	0.46±0.48 (0.23)	0.428	0.40±0.48 (0.22)	0.762

Values are presented as mean±SD (median).
* p Value compared with baseline.
ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; GDA, global disease activity assessment; RF, rheumatoid factor; SWS, stimulated whole salivary flow rate.

RESULTS

Patients

Between November 2008 and September 2009, 28 patients were included in the extension study of our randomised double-blind, placebo-controlled trial.[9] Baseline characteristics are shown in table 2.

Evaluation of change over time

ESSPRI revealed significant improvement (a reduction in patient symptoms) compared with baseline at 16, 24, 36 and 60 weeks after treatment with rituximab (table 3 and figure 1). ESSDAI showed significant improvement (a reduction in systemic complications) at weeks 16, 24 and 36. Results for each ESSDAI domain are given in table 4. All domains with some activity at baseline showed improvement, while most improvement was found in domains with highest activity at baseline. For patient's and physician's GDA, significant improvements were found at all time points (table 3 and figure 1). The RF level was significantly reduced at weeks 16, 24 and 36. SWS showed no improvements but also no decline of salivary flow at any time point.

Evaluation of internal responsiveness

As expected, SRM and ES for ESSPRI and ESSDAI were $\geq$0.8 at week 16 and decreased afterwards, with almost all scores being small at weeks 48 and 60 (table 5). SRM and ES were larger for ESSDAI than for ESSPRI, indicating better internal responsiveness for ESSDAI compared with ESSPRI. SRM and ES values for patient's and physician's GDA and RF broadly followed the pattern of ESSPRI and ESSDAI values. For SWS, both SRM and ES were small at all time points.

Physician's GDA, ESSDAI and RF level were able to detect flares; SRM and ES between week 16 and 60 were, respectively, 1.02 and 2.29 for physician's GDA, 0.82 and 1.67 for ESSDAI and 0.46 and 1.27 for RF level. The other measures showed less ability to detect flares (SRM/ES: ESSPRI 0.69/0.49; patient's GDA: -0.21/-0.13; SWS: -0.21/-0.13).

Evaluation of external responsiveness

At baseline and for most change scores, significant moderate to good correlations were observed between ESSPRI and patient's GDA, and between ESSDAI and physician's GDA (table 6), as expected. On the contrary, no clear relation was found between ESSPRI and ESSDAI or between these indices and RF and SWS.

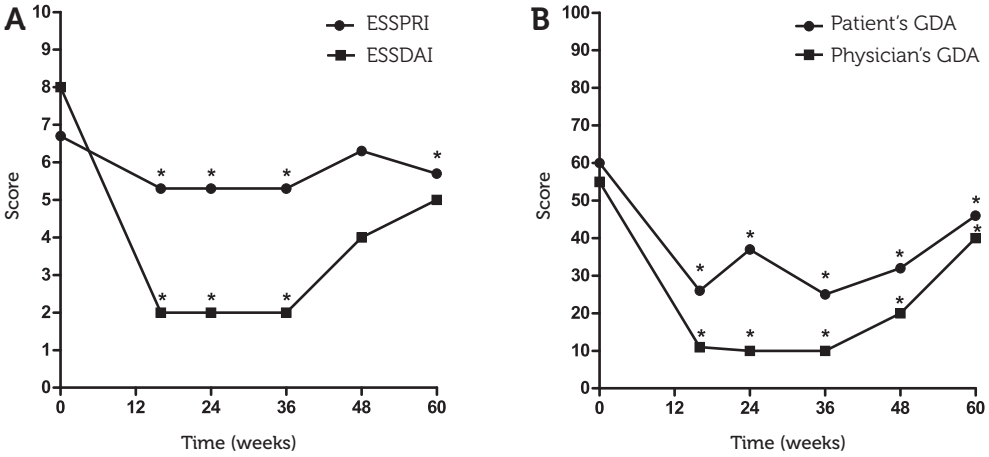

Figure 1. Disease activity in patients with primary Sjögren's syndrome treated with rituximab shown as median values. *p<0.05 compared with baseline. ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; GDA, global disease activity assessment.

DISCUSSION

To our knowledge, this is the first study to prospectively evaluate responsiveness of ESSPRI and ESSDAI in patients with pSS after intervention therapy. Internal and external responsiveness of ESSPRI and ESSDAI were good, which supports the usefulness of these indices in clinical trials.

The responsiveness of the recently developed ESSPRI[13] has not previously been reported, while retrospective validation of the ESSDAI has been performed in abstracted profiles of real patients with pSS with systemic complications.[17] The latter authors used the assessment whether a patient's condition had changed or not as an external anchor to assess internal responsiveness. The most widely used method to assess internal responsiveness, which can be applied in prospective studies, is to evaluate the change in a measure after treatment that has been shown to be efficacious.[24] However, studying responsiveness of disease activity indices in patients with pSS by evaluation after treatment is currently limited by the lack of standardised response criteria. Responsiveness can therefore only be evaluated at group level and not at the individual patient level.

In our study, ESSPRI, ESSDAI (improvement in all domains with some activity at baseline; most improvement in domains with highest activity at baseline), patient's and physician's GDA and RF improved significantly after treatment with rituximab. The duration of the beneficial effect differed for the various activity measures, but all measures showed improvements up to 36 weeks after treatment. These results are in line with the course of the subjective and objective improvements as reported by Meijer et al.[9,26] No improve-

Table 4. Disease activity for each ESSDAI domain.

Domain	Outcome	Baseline	Week 16	Week 24	Week 36	Week 48	Week 60
Constitutional	No/low/moderate, n	16/12/0	26/2/0	25/3/0	27/1/0	23/5/0	23/3/1
	No/low/moderate, %	57/43/0	93/7/0	89/11/0	96/4/0	82/18/0	85/11/4
Lymphadenopathy	No/low/moderate/high, n	28/0/0/0	28/0/0/0	28/0/0/0	28/0/0/0	28/0/0/0	26/1/0/0
	No/low/moderate/high, %	100/0/0/0	100/0/0/0	100/0/0/0	100/0/0/0	100/0/0/0	96/4/0/0
Glandular	No/low/moderate, n	11/15/2	27/1/0	25/3/0	24/4/0	23/5/0	17/10/0
	No/low/moderate, %	39/54/7	96/4/0	89/11/0	86/14/0	82/18/0	63/37/0
Articular	No/low/moderate/high, n	20/3/4/1	27/0/1/0	26/2/0/0	23/4/0/1	21/3/3/1	18/4/3/2
	No/low/moderate/high, %	71/11/14/4	96/0/4/0	93/7/0/0	82/14/0/4	75/11/11/4	67/15/11/7
Cutaneous	No/low/moderate/high, n	24/0/3/1	25/0/3/0	28/0/0/0	26/2/0/0	25/0/2/1	21/1/3/2
	No/low/moderate/high, %	86/0/11/4	89/0/11/0	100/0/0/0	93/7/0/0	89/0/7/4	78/4/11/7
Pulmonary	No/low/moderate/high, n	25/3/0/0	26/2/0/0	24/4/0/0	27/0/1/0	26/2/0/0	22/5/0/0
	No/low/moderate/high, %	89/11/0/0	93/7/0/0	86/14/0/0	96/0/4/0	93/7/0/0	82/19/0/0
Renal	No/low/moderate/high, n	27/1/0/0	27/1/0/0	27/1/0/0	27/1/0/0	27/0/1/0	26/1/0/0
	No/low/moderate/high, %	96/4/0/0	96/4/0/0	96/4/0/0	96/4/0/0	96/0/4/0	96/4/0/0
Muscular	No/low/moderate/high, n	28/0/0/0	28/0/0/0	28/0/0/0	28/0/0/0	27/0/0/1	26/1/0/0
	No/low/moderate/high, %	100/0/0/0	100/0/0/0	100/0/0/0	100/0/0/0	96/0/0/4	96/4/0/0
PNS	No/low/moderate/high, n	26/2/0/0	28/0/0/0	28/0/0/0	28/0/0/0	28/0/0/0	25/1/1/0
	No/low/moderate/high, %	93/7/0/0	100/0/0/0	100/0/0/0	100/0/0/0	100/0/0/0	93/4/4/0
CNS	No/low/high, n	28/0/0	28/0/0	28/0/0	28/0/0	28/0/0	27/0/0
	No/low/high, %	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0	100/0/0
Haematological	No/low/moderate/high, n	17/10/0/1	23/5/0/0	22/5/1/0	23/5/0/0	21/6/1/0	21/4/2/0
	No/low/moderate/high, %	61/36/0/4	82/18/0/0	79/18/4/0	82/18/0/0	75/21/4/0	78/15/7/0
Biological	No/low/moderate, n	4/10/14	11/8/9	12/7/9	11/9/8	12/9/7	12/6/9
	No/low/moderate, %	14/36/50	39/29/32	43/25/32	39/32/29	42/32/25	44/22/33

ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; PNS, peripheral nervous system; CNS, central nervous system.

Table 5. Internal responsiveness of disease activity measures in patients with primary Sjögren's syndrome treated with rituximab.

Standardised response mean (SRM)						
Time point	ESSPRI	ESSDAI	Patient's GDA	Physician's GDA	RF	SWS
Week 16	-0.86	-1.19	-0.97	-2.41	-0.80	0.25
Week 24	-0.68	-0.98	-0.73	-2.62	-0.78	0.24
Week 36	-0.53	-0.99	-0.94	-1.99	-0.65	0.10
Week 48	-0.27	-0.34	-0.83	-1.24	-0.20	0.18
Week 60	-0.29	-0.04	-0.49	-0.66	0.10	-0.13
Effect size (ES)						
Time point	ESSPRI	ESSDAI	Patient's GDA	Physician's GDA	RF	SWS
Week 16	-0.77	-1.13	-1.21	-2.36	-0.48	0.15
Week 24	-0.66	-1.11	-0.90	-2.65	-0.48	0.19
Week 36	-0.55	-1.13	-1.22	-2.41	-0.29	0.09
Week 48	-0.25	-0.60	-0.99	-1.78	-0.08	0.11
Week 60	-0.28	-0.05	-0.65	-1.01	0.09	-0.09

ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; GDA, global disease activity assessment; RF, rheumatoid factor; SWS, stimulated whole salivary flow rate.

ment in SWS was observed, which might be due to the long disease duration (median >5 years) of the subjects included in the trial. A longer disease duration is associated with less salivary secretory potential,[27] and the beneficial effect of rituximab on salivary flow of rituximab treatment is only observed in patients with a reasonable residual salivary flow.[5] Furthermore, there might still be a beneficial effect of rituximab on salivary gland function as no further decline of salivary flow was observed during follow-up, which commonly occurs in placebo-treated patients with pSS followed for a similar period of time.[9]

Responsiveness is an important measure for evaluating whether an instrument is able to detect changes as a result of treatment. Although the sample size of our study was relative small for assessing responsiveness, data were available for each patient at 6 different time points and showed consistent results.

Internal responsiveness was large for ESSDAI at weeks 16, 24 and 36 and decreased at weeks 48 and 60. This reduction in responsiveness is expected because B-cells are returning and the effect of rituximab is fading.[9] Furthermore, ESSDAI was able to detect flares. SRM and ES values for ESSPRI broadly followed the pattern of ESSDAI, but ESSDAI detected changes in disease activity more accurately. In addition, ESSDAI is superior to ESSPRI in flare detection. This might be explained by the fact that ESSDAI is a composite measure of clinical signs and symptoms and laboratory results, while ESSPRI is composed of 3 questions on dryness, pain and fatigue. Nevertheless, since the sensitivity

Table 6. External responsiveness of disease activity measures in patients with primary Sjögren's syndrome treated with rituximab.

		ESSPRI					
Outcome		**Baseline**	**Δ0-16**	**Δ0-24**	**Δ0-36**	**Δ0-48**	**Δ0-60**
ESSDAI	ρ	-0.056	0.011	-0.010	0.117	0.088	0.139
	p	0.777	0.954	0.962	0.569	0.682	0.356
Patient's GDA	ρ	0.620	0.431	0.315	0.525	0.393	0.623
	p	0.000	0.022	0.110	0.006	0.058	0.001
Physician's GDA	ρ	0.349	0.088	0.255	0.116	0.062	0.103
	p	0.069	0.657	0.200	0.574	0.772	0.625
RF	ρ	0.090	0.117	0.187	0.306	0.379	0.324
	p	0.650	0.552	0.349	0.128	0.058	0.115
SWS	ρ	-0.036	-0.005	0.128	-0.174	-0.288	-0.285
	p	0.855	0.981	0.524	0.395	0.172	0.199
		ESSDAI					
Outcome		**Baseline**	**Δ0-16**	**Δ0-24**	**Δ0-36**	**Δ0-48**	**Δ0-60**
Patient's GDA	ρ	0.145	0.349	0.350	0.121	0.395	0.509
	p	0.463	0.068	0.068	0.539	0.037	0.007
Physician's GDA	ρ	0.378	0.389	0.435	0.500	0.743	0.736
	p	0.047	0.041	0.021	0.007	0.000	0.000
RF	ρ	-0.082	-0.122	-0.225	0.094	-0.141	-0.125
	p	0.677	0.536	0.250	0.635	0.476	0.533
SWS	ρ	-0.137	-0.203	0.029	0.175	-0.029	-0.066
	p	0.486	0.309	0.882	0.372	0.882	0.758

Δ0-16, change from baseline to 16 weeks; Δ0-24, change from baseline to 24 weeks; Δ0-36, change from baseline to 36 weeks; Δ0-48, change from baseline to 48 weeks; Δ0-60, change from baseline to 60 weeks. ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; GDA, global disease activity assessment; RF, rheumatoid factor; SWS, stimulated whole salivary flow rate.

to change of ESSPRI is reasonable, dryness, pain and fatigue apparently are important distinguishing features of the disease.

Physician's GDA showed large internal responsiveness and was able to detect flares. One might argue that this makes physician's GDA a better instrument to measure disease activity than ESSDAI, especially since physician's GDA is less time-consuming to complete. However, Seror et al[14] showed that physician's GDA has limited reliability because the influence of patient symptoms and signs on the physicians' evaluation of disease activity is extremely variable. Furthermore, in our study, physician's GDA was assessed by only 2 physicians, both of whom have extensive experience in this field. Finally, these physicians were not blinded for time points, which may also have influenced

their assessment. Therefore, it is thought that ESSDAI results in more objective, reliable and predictable outcome than physician's GDA in clinical trials.

The internal responsiveness of patient's GDA was also large, although flares were difficult to detect. The larger internal responsiveness observed for patient's GDA compared with ESSPRI might be related to the fact that patient's GDA measures more than patient's symptoms; for example, this measure is likely to be influenced by the effect of treatment on systemic signs.

As mentioned before, a limitation of studying external responsiveness of any disease activity index in patients with pSS is the lack of standardised response criteria. Therefore, it is not possible to use the receiver operating characteristic method to assess the ability of an index to reflect both change (in terms of sensitivity) and no change (in terms of specificity) on external response criteria.[24] In the present study, we therefore used correlation coefficients to assess external responsiveness. The correlations for ESSPRI and ESSDAI were promising. As expected, moderate correlations between ESSPRI and patient's GDA and between ESSDAI and physician's GDA were found, indicating that these indices indeed assess related but slightly different outcome constructs. A poor association was found between ESSPRI and ESSDAI. A possible explanation of this poor association is that, although both ESSPRI and ESSDAI improved after treatment, the weight given to a certain change by the physician and the patient is different. For example, a physician can rate an increase in salivary flow as very contributory, while the patient rates this increase in salivary flow only as satisfactory as his sensation of a dry mouth has only slightly improved. Another possible explanation of the poor association between ESSPRI and ESSDAI might be that ESSPRI and ESSDAI measure different domains of pSS. In our opinion, combining both indices would be preferable for use in clinical trials since both subjective (ESSPRI) and more objective (ESSDAI) measures are important for evaluating response to treatment.

In conclusion, this study demonstrated that ESSPRI and ESSDAI are sensitive indices to measure change in disease activity after therapeutic intervention, which supports their usefulness for future clinical trials in patients with pSS. Responsiveness of ESSDAI was more prominent than that of ESSPRI.

ACKNOWLEDGEMENTS

We would like to thank J Bulthuis-Kuiper for her assistance in collecting the data and Dr M Jalving for reading the manuscript and providing constructive criticism.

ETHICS APPROVAL

This study was conducted with the approval of the local ethics committee at the University Medical Center Groningen, The Netherlands (METc2008.179) and all patients provided written informed consent to participate in the study.

FUNDING

This investigator-driven study was financially supported by Roche, Woerden, The Netherlands, which supplied study medication. There was no involvement of the funding source in study design, patient recruitment, data collection, analysis and interpretation and writing of the report.

COMPETING INTEREST

None.

References

1 Hansen A, Lipsky PE, Dörner T. Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. Curr Opin Rhematol 2005;17:558-665.

2 Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology 2009;48:1077-82.

3 Kallenberg CG, Vissink A, Kroese FG, et al. What have we learned from clinical trials in primary Sjögren's syndrome about pathogenesis? Arthritis Res Ther 2011;13:205-12.

4 Vissink A, Bootsma H, Spijkervet FK, et al. Current and future challenges in primary Sjögren's syndrome. Curr Pharm Biotechnol 2012;13:2026-45.

5 Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005;52:2740-50.

6 Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjögren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007;57:310-17.

7 Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B-cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis 2007;66:351-57.

8 Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren's syndrome with rituximab: results of a randomised, double- blind, placebo controlled pilot study. Ann Rheum Dis 2008; 67:1541-44.

9 Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960-8.

10 Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjögren syndrome: a systematic review. JAMA 2010;304:452-60.

11 Vissink A, Kallenberg CG, Bootsma H. Treatment approaches in primary Sjögren's syndrome. JAMA 2010;304:2015-6.

12 Meiners PM, Vissink A, Kallenberg CG, Kroese FG, Bootsma H. Treatment of primary Sjögren's syndrome with rituximab. A feasible approach or just a starting point? Expert Opin Biol Ther 2011;63:1116-23.

13 Seror R, Ravaud P, Mariette X, et al. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a patient index for primary Sjögren's syndrome. Ann Rheum Dis 2011;70:968-72.

14 Seror R, Ravaud P, Bowman S, et al. EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI): development of a consensus systemic disease activity index in primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

15 Fortin PR, Stucki G, Katz JN. Measuring relevant change: an emerging challenge in rheumatologic clinical trials. Arthritis Rheum 1995;38:1027-30.

16 Guyatt G, Walter S, Norman G. Measuring change over time: assessing the usefulness of evaluative instruments. J Chronic Dis 1987;40:171-8.

17 Seror R, Mariette X, Bowman S, et al. Accurate detection of changes in disease activity in primary Sjögren's syndrome by the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. Arthritis Care Res 2010;62:551-8.

18 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.

19 Dawes C. Circadian rhythms in human salivary flow rate and composition. J Physiol 1972;220:529-45.

20 Ferguson DB, Fort A, Elliott AL, et al. Circadian rhythms in human parotid saliva flow rate and composition. Arch Oral Biol 1973;18:1155-73.

21 Burlage FR, Pijpe J, Coppes RP, et al. Accuracy of collecting stimulated human parotid saliva. Eur J of Oral Sci 2005;113:386-90.

22 Kalk WW, Vissink A, Stegenga B, et al. Sialometry and sialochemistry: a non-invasive approach for diagnosing Sjögren's syndrome. Ann Rheum Dis 2002;61:137-44.

23 Kalk WW, Vissink A, Spijkervet FK, et al. Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome. Ann Rheum Dis 2001;60:1110-6.

24 Husted JA, Cook RJ, Farewell VT, et al. Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol 2000;53:459-68.

25 Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27:S178-89.

26 Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren's syndrome: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5.

27 Pijpe J, Kalk WW, Bootsma H, et al. Progression of salivary gland dysfunction in patients with Sjögren's syndrome. Ann Rheum Dis 2007;66:107-12.

Chapter 5.2

EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomised controlled trial

Rada V Moerman[1], Suzanne Arends[1], Petra M Meiners[2], Liesbeth Brouwer[1], Fred KL Spijkervet[2], Frans GM Kroese[1], Arjan Vissink[2], Hendrika Bootsma[1]

Department of [1]Rheumatology and Clinical Immunology and [2]Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, The Netherlands

Ann Rheum Dis 2014;73:472-4

Rituximab therapy is a promising treatment for primary Sjögren's syndrome (pSS).[1,2] So far, treatment studies performed in patients with pSS lacked the use of a uniform outcome measure to monitor disease activity.

Recently, the European League Against Rheumatism (EULAR) developed the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).[3] ESSDAI was shown to be able to monitor disease activity in patient profile and open-label studies.[4,5] To further study the utility of ESSDAI for clinical studies, we assessed the responsiveness of ESSDAI after rituximab treatment in a randomised controlled trial (RCT) of patients with pSS.[6]

As the principal investigator (HB) was involved in the development of ESSDAI, the database of a single-center, randomised, double-blind, placebo-controlled trial (see reference 6 for details) was prospectively completed with regard to all ESSDAI domains, namely the cutaneous, respiratory, renal, articular, muscular, peripheral and central nervous system, haematological, glandular, constitutional, lymphadenopathy and biological domains. After completion of the RCT, an independent and blinded researcher (RM) assessed the medical records of all included patients (n=30) and calculated ESSDAI at baseline and at 5, 12, 24, and 48 weeks after treatment.

Generalised estimating equations were used to analyse ESSDAI over time within subjects and between treatment groups. Since the residuals were non-normally distributed, ESSDAI was square-root transformed before entering into the equation. Responsiveness of ESSDAI was assessed using standardised response mean (SRM) and effect size (ES).[7] SRM and ES <0.5 were interpreted as small, 0.5-0.8 as moderate and >0.8 as large. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, Illinois, USA). p Values <0.05 were considered statistically significant.

Median (range) ESSDAI at baseline were 8.0 (4-13) and 6.5 (2-13) in the rituximab and placebo group, respectively. In rituximab-treated patients, ESSDAI improved significantly compared with baseline up to 36 weeks after treatment and had returned to baseline values by week 48. In placebo-treated patients, a significant decrease in ESSDAI was found only at week 5 (figure 1). From 5 to 24 weeks, the evolution of ESSDAI scores over time was significantly different between rituximab-treated and placebo-treated patients. ESSDAI was significantly lower in the rituximab group compared with the placebo group at weeks 12 and 24, which demonstrates the effectiveness of rituximab in reducing disease activity.

In the rituximab group, SRM and ES for ESSDAI were large at weeks 5 to 24, moderate at week 36 and small at week 48 (table 1). This indicates that ESSDAI adequately reflects the transient effect of the rituximab with decreasing disease activity up to week 24 and relapse of the disease activity at week 48. In the placebo group, SRM and ES were moderate at week 5 and small at all other time points.

The present analysis demonstrates that ESSDAI is able to show significant changes in disease activity in patients with pSS treated with rituximab compared with placebo. These findings confirm the usefulness of ESSDAI for clinical studies, as suggested previously.[4,5]

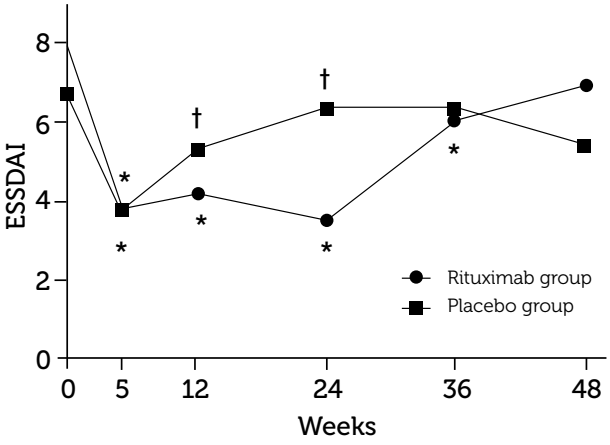

Figure 1. Median European League Against Rheumatism Sjogren's Syndrome Disease Activity Index (ESSDAI) scores of primary Sjogren's syndrome patients treated with rituximab (n=20) or placebo (n=10). *p<0.05 versus baseline †p<0.05 rituximab versus placebo.

The high responsiveness of ESSDAI at weeks 5 to 24 matches the results of changes in clinical and laboratory values, as reported before.[6] These parameters returned to baseline values within the same timeframe as ESSDAI after rituximab treatment. The significant decrease in ESSDAI as well as the moderate SRM and ES in the placebo group at week 5 are likely due to steroids (100 mg intravenous methylprednisolone, followed by an oral tapering of 2 days 60 mg, 2 days 30 mg and 1 day 15 mg prednisone) administered to minimise side effects of rituximab infusions.[6]

The large differences in responsiveness of ESSDAI between rituximab and placebo groups show that ESSDAI is a sensitive instrument to assess changes in disease activity over time. Based on the present data, ESSDAI at week 24 seems to be a good endpoint to assess treatment efficacy of rituximab. Overall, these results support the usefulness of ESSDAI in future clinical trials.

Table 1. Responsiveness of ESSDAI in patients with primary Sjögren's syndrome treated with rituximab (n=20) or placebo (n=10).

	Time point				
	Week 5	Week 12	Week 24	Week 36	Week 48
SRM					
ESSDAI rituximab	-1.11	-0.97	-1.04	-0.44	-0.20
ESSDAI placebo	-0.60	-0.39	0.07	0.15	-0.18
ES					
ESSDAI rituximab	-1.09	-1.04	-1.15	-0.50	-0.26
ESSDAI placebo	-0.60	-0.37	0.06	0.10	-0.18

SRM and ES <0.5 were interpreted as small, 0.5-0.8 as moderate and >0.8 as large.
ES, effect size; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; EULAR, European League Against Rheumatism; pSS, primary Sjögren's syndrome; SRM, standardised response mean.

References

1 Meiners PM, Vissink A, Kallenberg CG, et al. Treatment of primary Sjögren's syndrome with anti-CD20 therapy (rituximab). A feasible approach or just a starting point? Expert Opin Biol Ther 2011; 11:1381-94.

2 Ramos-Casals M, Tzioufas AG, Stone JH, et al. Treatment of primary Sjögren syndrome: a systematic review. JAMA 2010;304:452-60.

3 Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-1109.

4 Seror R, Mariette X, Bowman S, et al. Accurate detection of changes in disease activity in primary Sjögren's syndrome by the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. Arthritis Care Res (Hoboken) 2010;62:551-8.

5 Meiners PM, Arends S, Brouwer E, et al. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012;71:1297-302.

6 Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960-8.

7 Husted JA, Cook RJ, Farewell VT, et al. Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol 2000;53:459-68.

Chapter 6

Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study)

Petra M Meiners[1], Arjan Vissink[1], Frans GM Kroese[2], Fred KL Spijkervet[1], Nicole Sillevis Smitt-Kamminga[3], Wayel H Abdulahad[2], Janita Bulthuis-Kuiper[2], Liesbeth Brouwer[2], Suzanne Arends[2], Hendrika Bootsma[2]

Departments of [1]Oral and Maxillofacial Surgery, [2]Rheumatology and Clinical Immunology, and [3]Opthalmology, University of Groningen, University Medical Center Groningen, The Netherlands

Abatacept treatment reduces disease activity in early Sjögren's syndrome (open-label proof of concept ASAP study)

Edited version of: Ann Rheum Dis 2014 doi: 10.1136/annrheumdis-2013-204653 [Epub ahead of print]

ABSTRACT

Objective: To assess the efficacy and safety of abatacept in patients with early and active primary Sjögren's syndrome (pSS).

Methods: All 15 patients (12 women, 3 men) included in the open-label Active Sjögren Abatacept Pilot (ASAP) study met the revised American-European Consensus Group criteria for pSS. All patients were biological disease-modifying antirheumatic drug (DMARD) naive. If applicable, treatment with traditional DMARDs, hydroxychloroquine or corticosteroids had been discontinued at least one month before baseline. Patients were treated with 8 abatacept infusions administered intravenously on days 1, 15, and 29 and every 4 weeks thereafter (total treatment period of 24 weeks). Follow-up was conducted at 4, 12, 24 (on treatment), 36 and 48 weeks (off treatment). Disease activity was assessed with European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) and EULAR Sjögren Syndrome Patient Reported Index (ESSPRI). Several other functional, laboratory and subjective variables were analysed. Generalised estimating equations were used to analyse parameters over time within patients.

Results: ESSDAI, ESSPRI, rheumatoid factor and IgG levels decreased significantly during abatacept treatment and increased post-treatment. Salivary and lacrimal gland function did not change during treatment. Fatigue and health-related quality of life (HR-QoL) improved significantly during treatment. No serious side effects or infections were seen.

Conclusions: In this open-label proof of concept study, abatacept treatment is effective, safe and well tolerated and results in improved disease activity, laboratory parameters, fatigue and HR-QoL in patients with early and active pSS.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized primarily by chronic inflammation of exocrine glands, in particular salivary and lacrimal glands. The pathognomonic histological finding in salivary gland biopsies is progressive focal infiltration of B- and T-cells, together with other non-lymphoid mononuclear cells around the striated ducts.[1] This inflammatory process leads to changes in exocrine function and destruction of the salivary glands in longstanding pSS. In turn, these changes result in a variety of complaints, the most common of which are dry mouth and dry eyes. Any other organ may also be affected by the inflammatory process, leading to extraglandular manifestations such as arthritis, vasculitis, nephritis and pulmonary involvement.[2] Almost all patients suffer from fatigue and may be restricted in their daily activities and their participation in society, resulting in reduced health-related quality of life (HR-QoL) and impaired socio-economic status.[3] Overall, SS is a disabling disease and there is a clear need for development of adequate treatment modalities to reduce SS-related symptoms and to halt progression of the disease.

Traditional disease-modifying antirheumatic drugs (DMARDs) have limited effects in primary SS (pSS).[4] Biological agents that target specific cells or cytokines involved in immune responses have been introduced in the treatment of various systemic autoimmune diseases. No biological agent has yet been approved for the treatment of pSS. TNF-α inhibitors,[5-7] IFNα,[8] B-cell depletion therapy (anti-CD20 (rituximab)[9-12] and anti-CD22 (epratuzumab)[13]) have been studied in pSS, of which B-cell depleting therapy with rituximab showed the most promising results.[14]

Abatacept is a fully human fusion molecule of IgG-Fc and cytotoxic T-lymphocyte antigen 4 that modulates CD28-mediated T-cell co-stimulation. Co-stimulation between antigen-presenting cells and T-cells, and between B-cells and T-cells is an essential step in T-cell-dependent immune responses including autoimmune responses. Given the mechanism of action of abatacept and the recognised role of T-cells and B-cells (cellular and humoral response) in pSS, selective modulation of co-stimulation represents a rational therapeutic option in pSS. Because abatacept is a fully human biological agent, it may even have fewer side effects than chimeric agents such as rituximab, the latter use has resulted in serum sickness-like disease in some pSS patients.[14] Abatacept demonstrated consistently good safety and efficacy profiles in rheumatoid arthritis (RA)[15-18] and polyarticular juvenile idiopathic arthritis.[19] Although randomised controlled trials (RCTs) in systemic lupus erythematosus initially did not meet the pre-specified primary endpoints, post hoc analyses using alternative definitions for clinical response suggested possible beneficial effects in active lupus arthritis and proliferative nephritis.[20]

As a whole, these findings indicate that abatacept could be effective in pSS. The aim of this open-label proof of concept study was to investigate the efficacy and safety of abatacept in patients with early and active pSS.

METHODS

Study design

The Active Sjögren Abatacept Pilot (ASAP) study, a prospective, single-center, open-label proof of concept study, was performed in 15 pSS patients. The study protocol was approved by the institutional review board of the University Medical Center Groningen (METc2009.371). All patients provided written informed consent.

Patients

All 15 patients in the ASAP study fulfilled the revised American-European Consensus Group (AECG) criteria for pSS.[21] Eligibility criteria were: disease duration ≤5 years, stimulated whole salivary flow rate of ≥0.10 mL/minute and positivity for autoantibodies (rheumatoid factor (RF) ≤10 kIU/L and presence of anti-LA/SSA and/or anti-Ro/SSB autoantibodies in serum). In addition, results from a parotid salivary gland biopsy performed within 12 months before inclusion and showing characteristic features of SS had to be available.[22]

Patients who were previously treated with any biological DMARD were excluded. Furthermore, to be eligible for the study, traditional DMARDs, prednisone and hydroxychloroquine had to be discontinued for at least one month before baseline in patients using these drugs. Patients were allowed to use symptomatic medication for sicca symptoms and non-steroidal anti-inflammatory drugs. During the study, female patients were asked to use reliable methods of contraception.

All patients underwent electrocardiography and chest radiography at baseline. Patients with a history of any malignancy or with underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases, or with immune deficiency were excluded.

Drug administration

Abatacept was mixed into 0.9% normal saline and administered at the day care clinic by 30-minute intravenous infusion on days 1, 15, and 29, and then every 4 weeks (total treatment period 24 weeks). Dosing was approximately 10 mg/kg of body weight according to the patient's weight range at study entry, as follows: 500 mg for weight <60 kg, 750 mg for weight of 60-100 kg, and, 1000 mg for weight >100 kg (same as RA protocol).

Efficacy assessments

Definition of endpoints. Disease activity over time was assessed with ESSDAI, a validated systemic disease activity index to assess systemic complications of pSS, and ESSPRI, a patient-administered questionnaire to assess patient symptoms (dryness, pain and fatigue).[23-28] Other endpoints included salivary and lacrimal function tests, laboratory tests and subjective measurements of fatigue and HR-QoL. All variables were assessed at

baseline (within 4 weeks before first infusion with abatacept), at 4, 12 and 24 weeks (on treatment) and at 36 and 48 weeks (off treatment).

Disease activity. Besides ESSDAI and ESSPRI, a 100-mm visual analogue scale was used for rating global disease activity (GDA) by both the attending rheumatologist and the patient.

Salivary gland function. (Un)stimulated whole, parotid and submandibular/sublingual saliva samples were collected in a standardised manner and at a fixed time of the day, in order to minimise fluctuations related to a circadian rhythm of salivary secretion[29,30] and composition. Glandular saliva was collected from both individual parotid glands by use of Lashley cups, and submandibular/sublingual saliva was collected simultaneously by syringe aspiration from the area with the orifices of the submandibular excretory ducts. Unstimulated saliva was collected in the first 5 minutes, followed by collection of stimulated saliva after the salivary glands had been stimulated for 10 minutes. The salivary glands were stimulated with citric acid solution (2%), applied with a cotton swab to the lateral borders of the tongue every 30 seconds. Flow rates were calculated using the methods described by Kalk and colleagues.[31,32]

Lacrimal gland function. Lacrimal gland function was evaluated by unanaesthetised Schirmer's test and tear breakup time (TBUT).[33] Schirmer's test was carried out by placing a filter strip in the lower fornix of the conjunctiva of the eye. The amount of wetting was measured after 5 minutes. The TBUT is the interval between a complete blink and the appearance of the first randomly distributed dry spots and is assessed by instilling a 1% fluorescein solution in the fornix of both eyes. The patient was asked to blink a few times, after which the interval in seconds between the last blink and the first break in the tear film was measured.

Laboratory assessments. Laboratory tests included haematology, serum chemistry, serum RF and IgG levels and urinalysis.

Fatigue. Patients completed the Multidimensional Fatigue Inventory (MFI) to evaluate fatigue.[34] The MFI is a 20-item self-report instrument, which covers the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. Higher scores indicate a higher degree of fatigue.

HR-QoL. The Short Form-36 health survey (SF-36) was used to evaluate HR-QoL.[35] It contains 36 questions, evaluating 8 scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. Scales vary from 0 to 100, with 0 being the worst possible health status and 100 representing the best possible health status.

Safety assessments

All patients were evaluated for adverse events (AE), serious AE (SAE), clinically relevant changes in vital signs and laboratory test abnormalities. AE and SAE were classified according to the Medical Dictionary for Regulatory Activities (V.14.0). Injection and infusion

Table 1. Baseline characteristics of the ASAP study population.

Variable	Median (IQR) or n (%)
Age (years)	43 (32-51)
Female gender, n (%)	12 (80)
Disease duration (months)	11 (7-36)
IgG (g/L)	20.2 (15.3-26.7)
RF (kIU/L)	43 (20-184)
Anti-Ro / SSA positive, n (%)	15 (100)
Anti-La / SSB positive, n (%)	12 (80)
UWS (mL/minute)	0.12 (0.07-0.23)
SWS (mL/minute)	0.39 (0.24-0.57)
ESSDAI	11 (8-14)
Articular domain, n (%)§	13 (87)
Biological domain, n (%)§	11 (73)
CNS domain, n (%)§	0 (0)
Constitutional domain, n (%)§	5 (33)
Cutaneous domain, n (%)§	4 (27)
Glandular domain, n (%)§	11 (73)
Haematological domain, n (%)§	2 (13)
Lymphadenopathy domain, n (%)§	1 (7)
Muscular domain, n (%)§	0 (0)
PNS domain, n (%)§	1 (7)
Pulmonary domain, n (%)§	3 (20)
Renal domain, n (%)§	0 (0)
ESSPRI	7.5 (6.0-8.0)
Use of artificial tears, n (%)	15 (100)
Use of artificial saliva, n (%)	1 (7)
Use of prednisone, n (%)#	1 (7)
Use of hydroxychloroquine, n (%)#	2 (13)

Values are presented as median (IQR) unless otherwise indicated.
§Number (%) of patients having any degree of activity per ESSDAI domain (score of at least 1).
#Discontinued before study entry.
ASAP, Active Sjögren Abatacept Pilot; RF, rheumatoid factor; UWS, unstimulated whole salivary flow rate; SWS, stimulated whole salivary flow rate; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; CNS, central nervous system; PNS, peripheral nervous system; ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index.

reactions were prespecified and classified as injection site reactions (AE at the site of injection), acute infusion AE (occurring within 1 hour of the start of intravenous infusion), late AE (occurring after 1 hour of the start of infusion), and infections and infestations.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, Illinois, USA). Generalised estimating equations (GEE) were used to analyse disease activity,

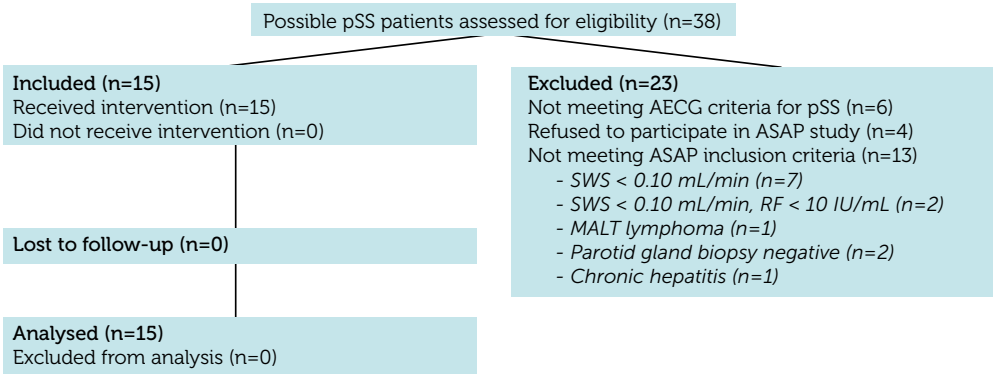

Figure 1. Inclusion of patients with pSS in the Active Sjögren Abatacept Pilot (ASAP) study. Based on last available sialometry, anti-La/SSA and anti-Ro/SSB positivity and RF data, 44 patients that were likely to be having pSS and to meet the ASAP inclusion criteria were approached. Six patients refused to participate in screening for the ASAP study. Therefore, 38 patients were assessed for eligibility. AECG, American-European Consensus Group; SWS, stimulated whole salivary flow rate; MALT, mucosa associated lymphoid tissue.

functional, laboratory, and subjective assessments over time within subjects. Data from baseline up to week 24 were used to assess change over time compared with baseline during treatment. Data from week 24 up to week 48 were used to assess change over time compared with week 24 during the post-treatment period. In case residuals were non-normally distributed, parameters were transformed (log, square root or logit) before being entered into the equation. p Value <0.05 was considered statistically significant.

RESULTS

Inclusion of 15 patients was completed between August 2010 and May 2012 (figure 1). All patients completed the treatment (baseline to week 24) and post-treatment (week 24 to 48) period. One patient did not complete questionnaires (ESSPRI, MFI and SF-36) during this trial. Baseline characteristics of the study population are summarised in table 1. Patients were relatively young, with a median age of 43, predominantly women (80%) and had a median disease duration of 11 months. In retrospect, 1 patient had a disease duration ≥5 years at the time of inclusion; however, none of the outcomes changed significantly by this patient. Three patients used medication (prednisone n=1, hydroxychloroquine n=2) which was discontinued at least 1 month before study entry according to the inclusion criteria.

Table 2. Results of disease activity, glandular function and laboratory assessments in pSS patients treated with abatacept.

Variable	Wk 0	Wk 4	Wk 12	Wk 16	Wk 24	Wk 36	Wk 48
ESSDAI	11±5 (11)	6±4 (6)*	6±8 (3)*	-	3±3 (2)*	10±6 (7)#	14±8 (11)#
ESSDAI, domains							
Articular domain, n (%)§	13 (87)	9 (60)	6 (40)	-	3 (20)	10 (67)	11 (73)
Biological domain, n (%)§	11 (73)	10 (67)	7 (47)	-	7 (47)	9 (60)	10 (67)
Constitutional domain, n (%)§	5 (33)	1 (7)	0 (0)	-	1 (7)	4 (27)	7 (47)
Cutaneous domain, n (%)§	4 (27)	2 (13)	4 (27)	-	1 (7)	3 (20)	4 (27)
Glandular domain, n (%)§	11 (73)	9 (60)	3 (20)	-	2 (13)	8 (53)	9 (60)
Haematological domain, n (%)§	2 (13)	4 (27)	3 (20)	-	4 (27)	2 (13)	10 (67)
Lymphadenopathy domain, n (%)§	1 (7)	0 (0)	1 (7)	-	1 (7)	3 (20)	4 (27)
PNS domain, n (%)§	1 (7)	0 (0)	0 (0)	-	0 (0)	2 (13)	1 (7)
Pulmonary domain, n (%)§	3 (20)	2 (13)	4 (27)	-	1 (7)	2 (13)	5 (33)
ESSPRI	7.0±1.5 (7.5)	6.0±1.7 (6.0)*	5.6±1.6 (6.0)*	-	5.8±2.3 (5.8)*	5.7±2.2 (5.7)	6.6±1.8 (7.0)
ESSPRI, subscales							
Dryness	6.5±2.0 (7.0)	5.9±2.0 (6.5)	5.9±2.1 (6.5)		6.5±2.0 (7.0)	5.6±2.5 (6.5)#	7.0±2.0 (7.5)
Pain	6.6±2.8 (7.5)	5.3±2.7 (6.0)*	4.5±2.7 (4.5)*		4.9±3.5 (5.0)*	4.9±3.1 (4.5)	5.6±2.8 (6.0)
Fatigue	7.8±1.1 (8.0)	6.7±2.1 (7.5)*	6.5±2.1 (7.0)*		5.9±2.8 (7.0)*	6.6±2.3 (7.0)	7.1±1.8 (7.5)
Patient's GDA	59±15 (58)	53±19 (53)	48±21 (50)*	-	48±26 (54)	54±24 (53)	59±23 (65)
Physician's GDA	46±8 (45)	36±14 (34)*	31±10 (36)*	-	33±18 (28)*	42±19 (43)#	48±15 (48)#
SWS (mL/minute)	0.43±0.25 (0.39)	0.47±0.39 (0.34)	0.50±0.31 (0.56)	-	0.41±0.33 (0.24)	0.38±0.26 (0.32)	0.31±0.22 (0.28)#
UWS (mL/minute)	0.17±0.17 (0.12)	0.16±0.13 (0.15)	0.14±0.15 (0.08)	-	0.16±0.15 (0.10)	0.14±0.14 (0.10)	0.15±0.14 (0.11)
Parotid saliva, stimulated (mL/minute)	0.16±0.19 (0.08)	0.13±0.12 (0.10)	0.15±0.13 (0.13)	-	0.11±0.11 (0.07)	0.11±0.07 (0.12)	0.09±0.06 (0.07)
Schirmer's test (mm/5 minute)	9.8±6.7 (9.5)	10.4±8.8 (6.0)	12.4±11.1 (7.5)	-	8.9±8.5 (5.0)	9.6±8.2 (6.5)	8.3±10.9 (1.0)
TBUT (seconds)	8.1±1.9 (8.0)	8.0±2.3 (9.0)	8.1±2.7 (9.0)	-	8.0±2.4 (10.0)	7.5±2.9 (8.0)	6.7±3.0 (7.0)#
Rheumatoid factor (kIU/L)	89±94 (43)	72±73 (45)*	57±62 (35)*	56±6 (31)*	56±63 (28)*	82±113 (31)#	87±103 (36)#

IgG (g/L)	21.5±7.3 (20.2)	19±6.2 (17.1)*	19.1±8.3 (15.5)*	18.2±7.5 (16.5)*	18.2±7.2 (16.5)*	20.6±9.6 (17.2)#	21.1±10.3 (18.6)#
MFI							
General fatigue	17.0±2.6 (17.5)	14.6±4.2 (14.5)*	14.6±3.8 (14.5)*	-	14.6±5.5 (16.0)*	14.2±4.1 (14.5)	14.0±3.2 (13.0)
Physical fatigue	12.8±2.2 (13.0)	13.7±3.7 (14.0)	13.7±4.2 (14.0)	-	14.7±4.1 (16.0)*	14.4±4.0 (15.5)	12.4±2.1 (12.0)
Reduced activity	13.4±3.8 (13.0)	11.8±3.5 (12.0)	12.1±3.3 (11.0)	-	11.6±4.8 (11.0)	11.9±3.3 (12.0)	12.7±3.3 (12.5)
Reduced motivation	12.2±4.2 (12.0)	11.1±3.8 (11.5)	11.4±3.7 (11.0)	-	10.3±5.0 (10.0)*	11.6±4.6 (11.5)	11±3.6 (11.0)
Mental fatigue	10.5±4.5 (11.5)	10.9±3.4 (12.0)	11.3±4.6 (11.0)	-	11.6±5.6 (13.0)	10.6±4.0 (11.0)	12.1±2.1 (12.0)
SF-36							
Physical functioning	63.6±17.0 (62.5)	68.5±16.5 (70.0)	68.2±18.9 (75.0)	-	70.0±22.7 (70.0)	67.9±22.4 (72.5)	62.7±20.6 (60.0)
Role physical	19.6±32.8 (0.0)	30.4±38.2 (12.5)	37.5±38.9 (25.0)	-	32.1±42.1 (12.5)	35.7±42.4 (12.5)	30.4±42.9 (0.0)
Bodily pain	59.2±23.0 (56.1)	66.5±22.0 (67.3)*	70.6±22.4 (72.4)*	-	65.7±25.4 (67.3)	63.8±26.8 (67.3)	62.8±22.1 (62.2)
General health	35±20.6 (37.5)	39.6±20.0 (37.5)*	38.9±19.9 (35.0)	-	37.9±19.3 (35.0)	33.2±16.9 (30.0)	31.4±16.5 (30.0)#
Vitality	36.4±13.6 (40.0)	45.4±16.1 (47.5)*	47.1±19.0 (47.5)*	-	50.0±23.0 (45.0)*	45.7±21.8 (50.0)	39.6±20.0 (37.5)
Social functioning	50.0±22.5 (50.0)	60.7±27.2 (62.5)	65.2±24.1 (62.5)*	-	62.5±25.9 (68.8)*	58±24.8 (62.5)	52.7±22.6 (56.3)
Role emotional	69.0±44.3 (100.0)	71.8±35.6 (100.0)	71.4±46.9 (100.0)	-	81.0±33.9 (100.0)	76.2±40.1 (100.0)	69.0±42.3 (100.0)
Mental health	68.0±17.7 (74.0)	75.4±14.1 (80.0)	76.9±15.4 (82.0)*	-	73.1±17.9 (78.0)*	69.1±19.4 (66.0)	65.7±15.9 (70.0)

Values are presented as mean±SD (median).
* p<0.05 compared with baseline.
#p<0.05 compared with week 24.
[f]Number (%) of patients having any degree of activity per ESSDAI domain (score of at least 1). The domains with no activity during the complete trial (central nervous system, muscular and renal domain) are not shown.
ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; PNS, peripheral nervous system; ESSPRI, EULAR Sjögren's Syndrome Patients Reported Index; GDA, global disease activity scale; SWS, stimulated whole salivary flow rate; UWS, unstimulated whole salivary flow rate; TBUT, tear break-up time test; MFI, Multidimensional Fatigue Inventory; SF-36, Short Form-36 health survey.

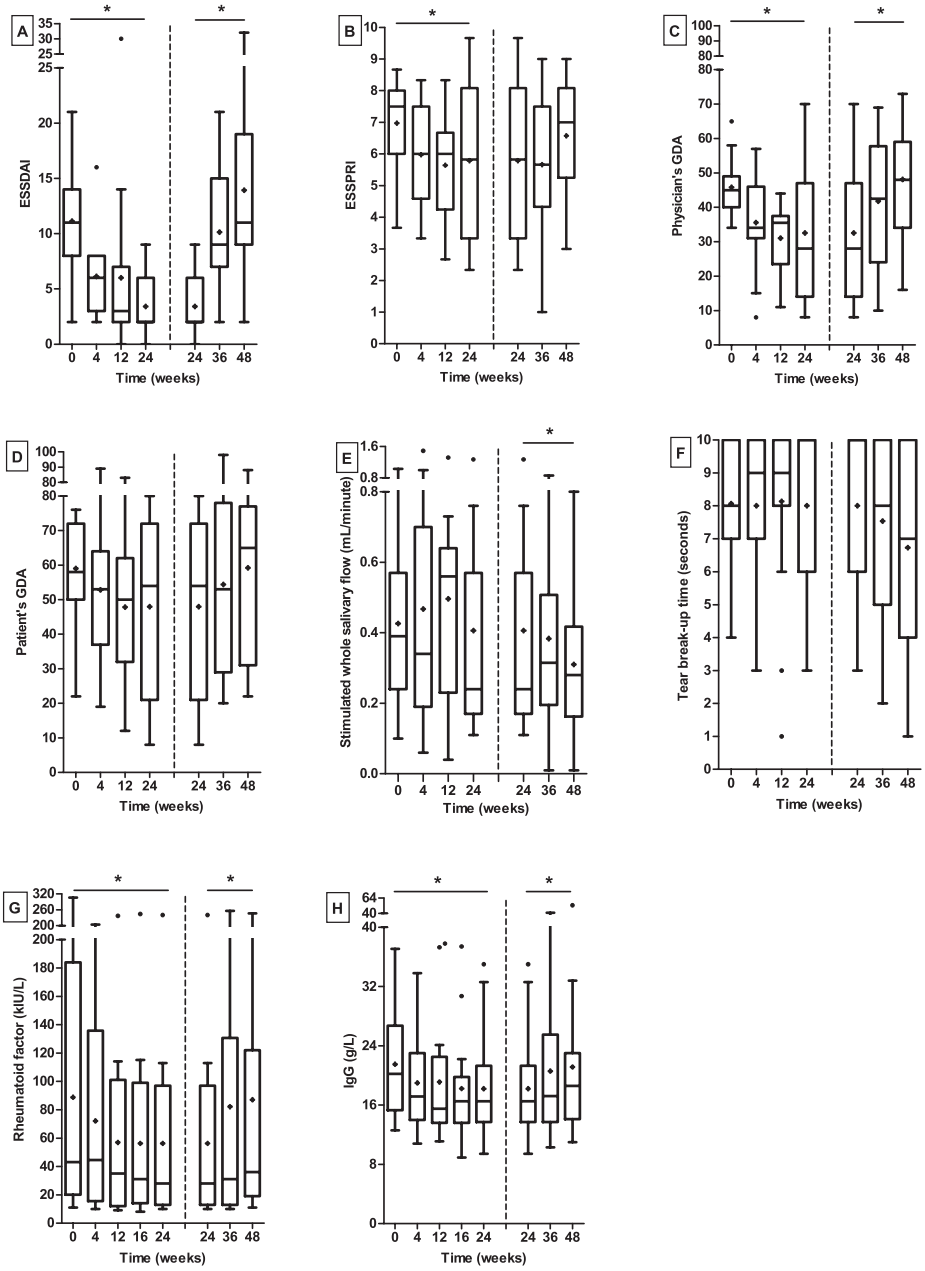

Figure 2. Change over time in pSS patients treated with abatacept during treatment (week 0-24) and off treatment (week 24-48). (A) ESSDAI, (B) ESSPRI, (C) physician's GDA, (D) patient's GDA, (E) stimulated whole salivary flow rate, (F) tear breakup time, (G) rheumatoid factor, (H) IgG. Box-and-whisker plots (Tukey); boxes=medians with interquartile ranges; +=means; whiskers=1.5 times the interquartile distances; •=outliers. *=p<0.05.

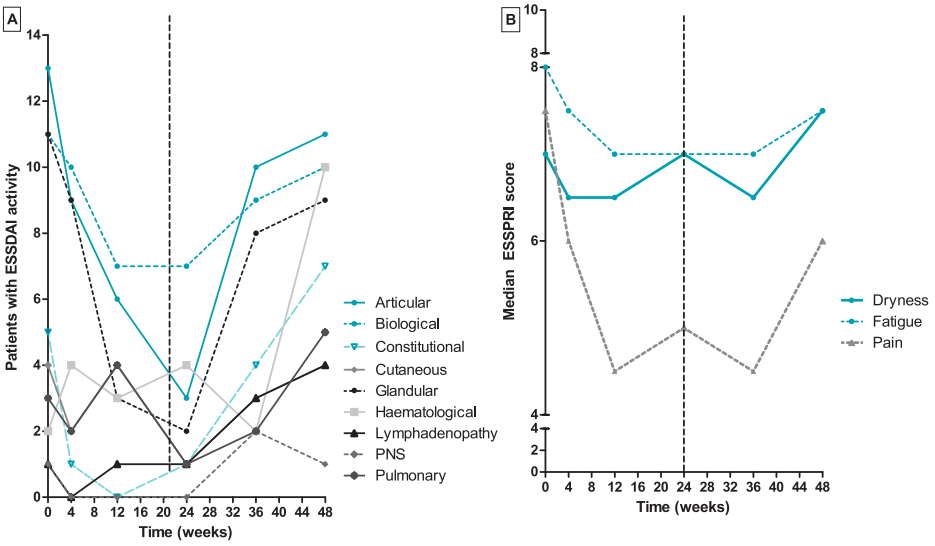

Figure 3. Change over time in scales of ESSPRI and domains of ESSDAI during treatment (week 0-24) and off treatment (week 24-48). (A) For ESSDAI, the number of patients having any degree of activity per ESSDAI domain (score of at least 1) are shown. The domains with no activity during the complete trial (central nervous system, muscular and renal domain) are not presented. (B) Median values are presented for ESSPRI. PNS, peripheral nervous system.

Efficacy

Disease activity. Treatment with abatacept resulted in a significant reduction of disease activity in pSS patients as established both with ESSDAI and ESSPRI (table 2). During treatment, median ESSDAI decreased from 11 (range 2-21) at baseline to 2 (range 0-9) 24 weeks after abatacept treatment ($p<0.001$). ESSDAI returned to baseline in the post-treatment period (weeks 24 to 48; $p<0.001$; figure 2A). ESSDAI at week 48 did not differ significantly from baseline ($p=0.137$). Additionally, we analysed the presence or absence of disease activity per ESSDAI domain (figure 3A). Most improvement was found in the articular, biological, constitutional and glandular domains. None of the patients had involvement of the muscular, renal or central nervous system domains of ESSDAI prior or during the study.

Median ESSPRI decreased from 7.7 (range 3.7-8.7) at baseline to 5.8 (range 2.3-9.7) at week 24 ($p=0.0015$), indicating a significant improvement in patient symptoms ($p=0.015$) during treatment. This was followed by a non-significant increase in ESSPRI in the post-treatment period ($p=0.151$; figure 2B). When looking at the scales of ESSPRI (dryness, pain and fatigue) individually, most improvement during abatacept treatment was seen on pain ($p=0.001$) and fatigue ($p=0.021$; figure 3B). In addition to ESSDAI and ESSPRI, reduced disease activity after abatacept treatment was further supported by the results of

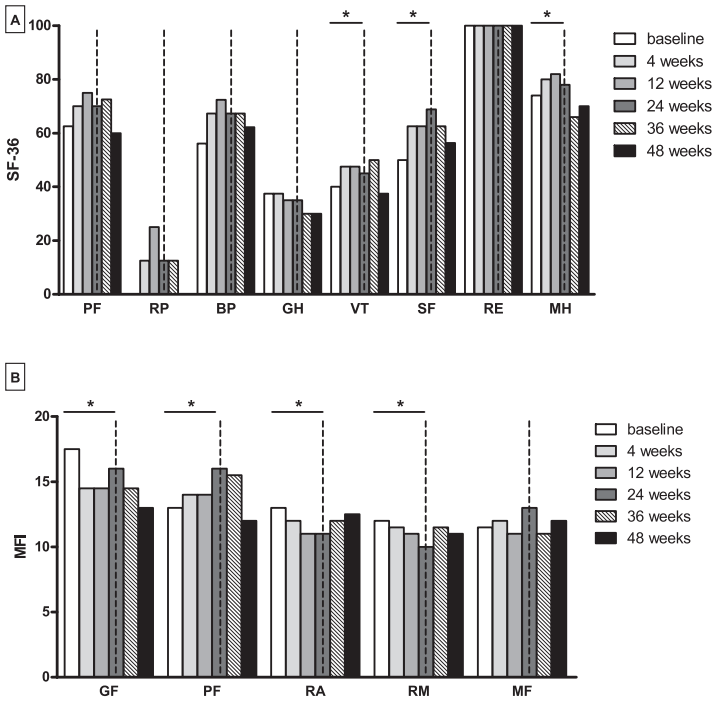

Figure 4. Health-related quality of life and fatigue during ASAP study. (A) Short Form-36 Health Survey (SF-36), (B) Multidimensional Fatigue Inventory (MFI). Median values are presented. *=p<0.05. SF-36: PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; PCS physical component summary; MCS, mental component summary; MFI: GF, general fatigue; PF, physical fatigue; RA, reduced activity; RM, reduced motivation; MF, mental fatigue.

the physician's and patient's GDA, which followed the same pattern of change as ESSDAI and ESSPRI (figures 2C and 2D).

Salivary gland function. Stimulated whole salivary flow rate (SWS) did not change during treatment, while a small but significant decrease (p=0.018) was seen post-treatment (figure 2E). Unstimulated whole salivary flow rate and parotid flow rate did not change, both on and off treatment.

Lacrimal gland function. Lacrimal gland function assessed with Schirmer's test and TBUT remained did not change during treatment. Post-treatment, Schirmer's test did not change, whereas TBUT showed a trend towards decrease in this period (p=0.108) (figure 2F).

Laboratory variables. Median RF level decreased significantly from 43 (range 11-306) at baseline to 28 (range 10-240) at week 24 (p=0.005) and IgG level decreased significantly from 20.2 (range 12.6-37.1) to 16.5 (range 9.4-35.0) during treatment (p=0.016). Both RF and IgG levels increased significantly in the post-treatment period (figures 2G and 2H).

Table 3. Adverse events observed in pSS patients during treatment with abatacept.

System organ classes	Events	Events (n)	Patients (n)
AEs (total)		*81*	*15*
Acute AEs (total)	*Total*	*17*	*6*
Gastrointestinal disorders	Nausea	2	2
General and infusion site conditions	Pyrexia	2	1
Nervous system disorders	Dizziness	7	4
Vascular disorders	Hypotension	4	3
	Flushing	2	1
Late AEs (total)	*Total*	46	*12*
Gastrointestinal disorders	Nausea	2	2
	Dyspepsia	1	1
	Aphthous stomatitis	5	2
General and infusion site conditions	Chills	1	1
	Astenia	1	1
	Influenza-like illness	1	1
	Fatigue	6	5
	Toothpain	1	1
Metabolism and nutrition disorders	Polydipsia	3	1
Investigations	Liver function test abnormal	1	1
Musculoskeletal/connective tissue disorders	Arthralgia	1	1
Nervous system disorders	Headache	13	7
	Dizziness	2	2
	Dyspnea	1	1
Respiratory, thoracic and mediastinal disorders	Cough	2	1
Skin and subcutaneous tissue disorders	Photosensitivity	2	2
	Rash	3	2
Infections and infestations	*Total*	*18*	*10*
	Tooth infection	1	1
	Viral upper airway infection	8	7
	Bacterial upper airway infection	5	3
	Folliculitis	1	1
	Oral candidiasis	1	1
	Vaginal candidiasis	1	1
	Onychomycosis	1	1

Fatigue. Patients receiving abatacept felt less tired during treatment. As mentioned before, the individual scale for fatigue of ESSPRI decreased significantly during treatment. When assessed with MFI in more detail, a reduction of fatigue during treatment was found for the scales general fatigue (p=0.009), reduced activity (p=0.011) and reduced motivation (p=0.013) (figure 4A). An increase was found for the scale physical fatigue (p=0.032).

HR-QoL. During treatment, there was a trend towards improved HR-QoL in most scales of SF-36, which reached significance for the scales vitality (p=0.001), social functioning (p=0.004) and mental health (p=0.015) (figure 4B).

Safety

A summary of AEs during treatment is presented in table 3. Overall, no abatacept-related deaths, cancers, opportunistic infections or atypical presentations of infections were observed during this trial. No SAEs occured, and no patients withdrew from the study due to AEs. One patient experienced a mild infusion reaction not requiring discontinuation of treatment.

Acute AEs. No injection site reactions occurred during treatment. Six patients (40% experienced acute AEs (in total 17 events); with dizziness and hypotension being the most commonly reported events. Acute AEs were usually mild in intensity. No severe acute infusion reactions were seen.

Late AEs. Twelve patients (80%) experienced late AEs (in total 46 events) during treatment, the most common of which were headache and fatigue.

Self-reported infections and infestations. During treatment, 18 self-reported infections were seen in 10 patients (67%), the most common being upper respiratory tract infections (viral and/or bacterial). None of the infections required hospitalisation. No unusual or opportunistic infections were seen.

Rescue medication. During treatment, 2 patients received rescue medication because they developed subacute cutaneous lupus after extreme sun exposure without protection. One patient was treated with steroids for 1 week (during week 10), while the other was treated with prednisone for 18 weeks (weeks 22 to 40).

DISCUSSION

In this open-label proof of concept study, abatacept treatment was shown to be effective and safe in early and active pSS. Disease activity assessed with ESSDAI, ESSPRI and physicians' GDA decreased, RF and IgG levels dropped, fatigue diminished and patients experienced improved HR-QoL. Salivary and lacrimal gland function did not change during treatment. No SAEs occurred; neither did patients withdraw from the study due to AEs. No unusual or opportunistic infections were seen.

To evaluate efficacy of new therapeutics such as abatacept, it is important to use adequate measures to quantify the extent and severity of the disease in a standardised way. Before the development of ESSDAI and ESSPRI such measures where lacking in pSS. In our previous clinical trials with rituximab, we therefore used significant improvement in SWS as our primary endpoint.[9,36,37] However, ESSDAI and ESSPRI were recently validated as tools to monitor disease activity.[25-28] Therefore, we now consider ESSDAI and ESSPRI as better measures for treatment effects.

Abatacept treatment resulted in a significant decrease in ESSDAI and ESSPRI. For ESSDAI, most improvement was found in the articular, biological, constitutional and glandular domains and for ESSPRI in pain and fatigue. Although we did not specifically include patients with high levels of systemic involvement or symptoms, our inclusion criteria resulted in a patient cohort with rather high ESSDAI and ESSPRI baseline values compared with a general pSS population.[25] This may be due to the willingness of patients who are severely impaired by their disease to participate in a clinical trial, or selection bias based on the required autoantibody positivity.

SWS provides a general indication of overall salivary secretory potential. In the present study, SWS did not change during abatacept treatment and a small but significant decrease was observed off-treatment. Lacrimal function also did not change during treatment with abatacept and showed a trend toward deterioration off-treatment. Therefore, although abatacept treatment may reduce deterioration of salivary and lacrimal gland function, it appeared to have a stronger effect on systemic manifestations during this limited observation period.

Thus far, the utility of abatacept for the treatment of pSS has been investigated in an open-label study in 11 pSS patients by Adler and coworkers.[38] Patients were treated following the same dosing regimen as our patients. In contrast to our study, none of their patients suffered from extraglandular disease and evaluation took place at baseline and 4 weeks after the last infusion (week 28), making comparisons difficult. Overall, their study demonstrated beneficial effects of abatacept treatment, namely, a slight increase in SWS (Saxon's test: from 1.61 g/2 minutes (baseline) to 1.74 g/2 minutes (week 28)), cellular changes and reduced inflammation in labial salivary glands. In contrast with our stable level of SWS during treatment, Adler and colleagues found a small increase in SWS assessed with another method (Saxon's test). This very small increase is probably clinically not relevant, since a change in SWS less than 25% can be explained by interindividual variation.[39] Regarding laboratory parameters, both the study by Adler et al and this study showed a decrease in IgG levels although this was not significant in the former. Beneficial effects on patients' symptoms were also described by Adler and coworkers, although no standardised description of the clinical effects of abatacept were given, e.g., evaluation of disease activity (ESSDAI and/or ESSPRI), fatigue or HR-QoL.[38]

Abatacept is an effective and safe treatment for RA. Some patients responded to abatacept within 2 to 4 weeks, but most adults responded within 12 to 16 weeks after initiation

of treatment and continued to improve when treated for 12 months.[40] In RA, anti-cyclic citrullinated peptide positivity was associated with better response to abatacept, independently of disease activity.[41] In our trial in pSS, amongst others, ESSDAI, ESSPRI, RF and IgG already showed significant improvements compared with baseline at week 4, with further improvement at weeks 12 and 24. Since all our patients were autoantibody positive (RF and anti-La/SSA and/or anti-Ro/SSB), the relation between the presence of autoantibodies and outcome could not be addressed. Finally, safety results in this trial with pSS patients were comparable with those found in RA patients.[15,18]

In conclusion, in this open-label proof of concept study, treatment with abatacept was effective, safe and well tolerated in active and early pSS patients. Abatacept treatment resulted in improved disease activity, laboratory parameters, fatigue and HR-QoL. The results of our study support the concept that T-cells play an important role in the pathophysiology of pSS. The promising results warrant confirmation in placebo-controlled RCTs in pSS.

ACKNOWLEDGEMENTS

We are grateful to Mattia AE Valente for reading the manuscript and providing constructive criticism.

FUNDING

This investigator-driven study was financially supported by Bristol Myers Squibb, Rueil Malmaison, France, which also supplied study medication. There was no involvement of this funding source in study design, patient recruitment, data collection, analysis and interpretation and writing of the report.

COMPETING INTERESTS

None of the authors have financial interests that could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

References

1 Abdulahad WH, Kroese FG, Vissink A, Bootsma H. Immune regulation and B-cell depletion therapy in patients with primary Sjögren's syndrome. J Autoimmun 2012;39:103-11.

2 Hansen A, Lipsky PE, Dorner T. Immunopathogenesis of primary Sjögren's syndrome: implications for disease management and therapy. Curr Opin Rheumatol 2005;17:558-65.

3 Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology (Oxford) 2009;48:1077-82.

4 Ramos-Casals M, Brito-Zeron P, Siso-Almirall A, et al. Topical and systemic medications for the treatment of primary Sjögren's syndrome. Nat Rev Rheumatol 2012;8:399-411.

5 Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomised, controlled trial of remicade in primary Sjögren's syndrome (TRIPSS). Arthritis Rheum 2004;50:1270-6.

6 Zandbelt MM, de Wilde P, van Damme P, et al. Etanercept in the treatment of patients with primary Sjögren's syndrome: a pilot study. J Rheumatol 2004;31:96-101.

7 Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjögren's syndrome: a twelve-week randomised, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004;50:2240-5.

8 Cummins MJ, Papas A, Kammer GM, et al. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. Arthritis Rheum 2003;49:585-93.

9 Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled trial. Arthritis Rheum 2010;62:960-8.

10 Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis 2008;67:1541-4.

11 Gottenberg JE, Cinquetti G, Larroche C, et al. Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and rituximab registry. Ann Rheum Dis 2013;72:1026-31.

12 St Clair EW, Levesque MC, Prak ET, et al. Rituximab therapy for primary Sjögren's syndrome: an open-label clinical trial and mechanistic analysis. Arthritis Rheum 2013;65:1097-106.

13 Carnahan J, Wang P, Kendall R, et al. Epratuzumab, a humanized monoclonal antibody targeting CD22: characterization of in vitro properties. Clin Cancer Res 2003;9:3982S-90S.

14 Meiners PM, Vissink A, Kallenberg CG, et al. Treatment of primary Sjögren's syndrome with anti-CD20 therapy (rituximab). A feasible approach or just a starting point? Expert Opin Biol Ther 2011;11:1381-94.

15 Kremer JM, Russell AS, Emery P, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis 2011;70:1826-30.

16 Bathon J, Robles M, Ximenes AC, et al. Sustained disease remission and inhibition of radiographic progression in methotrexate-naive patients with rheumatoid arthritis and poor prognostic factors treated with abatacept: 2-year outcomes. Ann Rheum Dis 2011;70:1949-56.

17 Schiff M, Keiserman M, Codding C, et al. Clinical response and tolerability to abatacept in patients with rheumatoid arthritis previously treated with infliximab or abatacept: open-label extension of the ATTEST study. Ann Rheum Dis 2011;70:2003-7.

18 Genovese MC, Schiff M, Luggen M, et al. Longterm safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy. J Rheumatol 2012;39:1546-54.

19 Ruperto N, Lovell DJ, Quartier P, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis.

Arthritis Rheum 2010;62:1792-802.

20 Mok CC. Abatacept for systemic lupus erythematosus: the outlook. Expert Opin Biol Ther 2012;12:1559-61.

21 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. Ann Rheum Dis 2002;61:554-8.

22 Pijpe J, Kalk WW, van der Wal JE, et al. Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46:335-41.

23 Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

24 Seror R, Ravaud P, Mariette X, et al. EULAR Sjögren's syndrome patient reported index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. Ann Rheum Dis 2011;70:968-72.

25 Seror R, Mariette X, Bowman S, et al. Accurate detection of changes in disease activity in primary Sjögren's syndrome by the European league against rheumatism Sjögren's syndrome disease activity index. Arthritis Care Res (Hoboken) 2010;62:551-8.

26 Meiners PM, Arends S, Brouwer E, Spijkervet FK, Vissink A, Bootsma H. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012;71:1297-302.

27 Seror R, Gottenberg JE, Devauchelle-Pensec V, et al. ESSDAI and ESSPRI: EULAR indexes for a complete picture of primary Sjögren's syndrome patients. Arthritis Care Res (Hoboken) 2013;65:1358-64.

28 Moerman RV, Arends S, Meiners PM, et al. EULAR Sjögren's syndrome disease activity index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomised controlled trial. Ann Rheum Dis 2014;73:472-4.

29 Dawes C. Circadian rhythms in human salivary flow rate and composition. J Physiol 1972;220:529-45.

30 Ferguson DB, Fort A, Elliott AL, et al. Circadian rhythms in human parotid saliva flow rate and composition. Arch Oral Biol 1973;18:1155-73.

31 Kalk WW, Vissink A, Stegenga B, et al. Sialometry and sialochemistry: a non-invasive approach for diagnosing Sjögren's syndrome. Ann Rheum Dis 2002;61:137-44.

32 Kalk WW, Vissink A, Spijkervet FK, Bootsma H, Kallenberg CG, Nieuw Amerongen AV. Sialometry and sialochemistry: diagnostic tools for Sjögren's syndrome. Ann Rheum Dis 2001;60:1110-6.

33 Kalk WW, Mansour K, Vissink A, et al. Oral and ocular manifestations in Sjögren's syndrome. J Rheumatol 2002;29:924-30.

34 Smets EM, Garssen B, Bonke B, et al. The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315-25.

35 Ware JE,Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care 1992;30:473-83.

36 Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjögren's syndrome: an open-label phase II study. Arthritis Rheum 2005;52:2740-50.

37 Meijer JM, Pijpe J, Vissink A, et al. Treatment of primary Sjögren syndrome with rituximab: extended follow-up, safety and efficacy of retreatment. Ann Rheum Dis 2009;68:284-5.

38 Adler S, Korner M, Forger F, et al. Evaluation of histological, serological and clinical changes in response to abatacept treatment of primary Sjögren's syndrome: a pilot study. Arthritis Care Res (Hoboken) 2013 [Epub ahead of print].

39 Burlage FR, Pijpe J, Coppes RP, et al. Accuracy of collecting stimulated human parotid saliva. Eur J of Oral Sci 2005;113:386-90.

40 Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for

the treatment of rheumatic diseases, 2012. Ann Rheum Dis 2013;72:2-34.

41 Gottenberg JE, Ravaud P, Cantagrel A, et al. Positivity for anti-cyclic citrullinated peptide is associated with a better response to abatacept: data from the 'orencia and rheumatoid arthritis' registry. Ann Rheum Dis 2012;71:1815-9.

Chapter 7

Summary and general discussion

SUMMARY

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized primarily by chronic inflammation of the exocrine glands. The salivary and lacrimal glands are most commonly affected, resulting in dry mouth and dry eyes. Extraglandular involvement can occur in SS, and includes, amongst others, pulmonary disease, renal disease and vasculitis. Moreover, almost all patients suffer from fatigue. SS can be primary (pSS) or secondary (sSS), the latter being associated with other autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). SS, is after RA, the most common systemic autoimmune disease, affecting about 0.3-1.0% of the general population, although it has received far less research and therapeutic attention than, for example, RA and SLE.[1] Whereas for RA a wide variety of traditional Disease-Modifying Antirheumatic Drugs (DMARDs) and biological DMARDs is available, systemic therapeutic options for SS are still limited and effective biological DMARDs are not yet approved.[2] This thesis covers several topics of SS, including (1) the impact of having SS on patients' functioning and daily activity, in order to underline the necessity to develop novel treatment options in SS, and (2) an assessment of the efficacy of 2 promising biological therapies (rituximab and abatacept) in the treatment of pSS. The effect of these biological DMARDs was studied in pSS patients and not in sSS patients, as in sSS patients there is always another autoimmune disorder present which may influence the treatment outcome of the biological DMARD studied. Furthermore (3), since it is crucial to quantify the extent and severity of pSS in a standardised way, we also evaluated the ability of European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI)[3] and EULAR Sjögren's syndrome Patient Reported Index (ESSPRI)[4] to monitor the effect of intervention treatment in pSS.

In **Chapter 2** a study is presented in which the health-related quality of life (HR-QoL), employment and disability in pSS and sSS patients is compared with the general Dutch population (matched for gender and age). HR-QoL, employment and disability were assessed in pSS and sSS patients regularly attending the University Medical Center Groningen (n=235). Response rate was 83%. The results revealed that SS patients scored lower HR-QoL, were less often employed and had higher disability rates than the general Dutch population. Patients with sSS scored lower on physical functioning, bodily pain and general health than pSS patients. This study showed that both pSS and sSS have a large impact on HR-QoL, employment and disability. These results underscore the necessity for the development of effective treatment of SS.

In **Chapter 3,** the management of glandular and extraglandular manifestations of SS is described and prospects for a better understanding of the progression and more effective treatment of SS are discussed. Although there is as yet no curative or causal

treatment for SS, various supportive and palliative treatment options are available, and targeted approaches (biological DMARDs) are in development or currently being tested in phase I, II or III trials. Although biological DMARDs are promising therapies, not all biological DMARDs that were effective in other autoimmune diseases such as RA appeared to be effective for the treatment of pSS. Randomised controlled trials (RCTs) failed to show a beneficial clinical effect of anti-TNF and IFN-α in pSS, whereas B-cell targeted therapy (both with anti-CD20 (rituximab) and anti-CD22 (epratuzumab)) seems promising. Other potential targets for biological therapy that have been suggested since then, include CD80/CD86 (abatacept), cytokines such as IL-1, IL-6 and BAFF (B-cell activating factor), adhesion molecules and chemokines. In the near future a large role for biological therapy for SS is expected. Larger phase II and III trials are needed to confirm the first promising findings of open-label studies and small RCTs with, e.g., rituximab (see **chapter 4**) and abatacept (see **chapter 6**).

In **chapter 4.1**, a study is described in which the efficacy and safety of B-cell depletion with rituximab was studied in a double-blind RCT in 30 pSS patients. Rituximab is a chimeric humanised monoclonal antibody specific for the B-cell surface molecule CD20, which is expressed on the surface of pre-B, transitional B- and mature B-lymphocytes, and is lost at the plasma cell stage. CD20 mediates B-cell activation, proliferation and differentiation.[5,6] CD20 may play an important role in the generation of T-cell independent antibody responses.[7] Possible mechanisms of cell lysis include antibody-dependant cellular cytotoxicity and complement-dependent cytotoxicity mechanisms. The antibody to CD20 also induces apoptosis of B-cells.[8] In this RCT, 20 patients were treated with rituximab, while 10 patients received placebo. All patients received an additional short course (5 days) of corticosteroids in order to prevent the development of side effects. Treatment with rituximab led to improvement of objective and subjective parameters of disease activity in pSS patients. Salivary gland function and laboratory parameters improved, fatigue diminished and extraglandular manifestations improved. Most improvements were seen 12 to 36 weeks after initial treatment.

Based on the promising results of the RCT with rituximab, an extension study was performed to study the efficacy of retreatment with rituximab (**chapter 4.2**). We analysed data of 15 pSS patients who received their first course of rituximab within our previously reported RCT (**chapter 4.1**) and the second course of rituximab during the following extension study. Retreatment with rituximab resulted in comparable beneficial effects as the initial treatment on objective parameters, including disease activity assessed with ESSDAI,[3] whereas the effect on patient-reported parameters was somewhat less pronounced. Because goals of retreatment include maintenance of efficacy and prevention of flare, further studies are needed to investigate optimal timing of retreatment of rituximab in pSS patients.

In **chapter 4.3**, the outcomes of the various open-label studies and RCTs in pSS patients

with rituximab that have been reported in the international literature between January 2000 and January 2011 are critically discussed. Both open-label studies and RCTs showed the efficacy of rituximab in reducing, amongst others, extraglandular manifestations and fatigue, and in increasing HR-QoL, whereas the increase in salivary flow is dependent on the residual function of the glands. The baseline level of salivary flow is related to disease duration, the shorter the disease duration the higher the residual salivary flow rate. Patients with early disease showed more improvements than patients with longer disease duration regarding, amongst others, oral and eye dryness, fatigue and HR-QoL. Histopathological findings underline the efficacy of B-cell depletion and indicate the potential for regeneration of glandular tissue in pSS. The main conclusion from this overview is that overall treatment with rituximab is promising, but that further studies are needed to select pSS patients that will benefit most from this therapy.

To evaluate effectiveness of (biological) DMARDs such as rituximab (see **chapter 4**) and abatacept (see **chapter 6**), it is important to use adequate measures to quantify the extent and severity of the disease in a standardised way. Two indices, the ESSDAI and ESSPRI, have recently been developed that might fulfill this role in pSS.[3,4] Prospective data on the responsiveness of ESSDAI after therapeutic intervention in pSS patients were, however, lacking. Furthermore, data on responsiveness of ESSPRI were not yet available. Therefore, the aim of the study presented in **chapter 5.1** was to evaluate the responsiveness of ESSDAI and ESSPRI in 28 patients with pSS who were treated with rituximab. This study showed that ESSDAI and ESSPRI are sensitive measures of change in disease activity after therapeutic intervention, which supports the usefulness of these indices for clinical trials in patients with pSS. Responsiveness of ESSDAI was greater than that of ESSPRI.
To further study the utility of ESSDAI for clinical studies, we assessed the responsiveness of ESSDAI in our double-blind RCT with rituximab in **chapter 5.2**. As the principal investigator was involved in the development of ESSDAI, the database of this trial was prospectively completed with regard to all ESSDAI domains. Large differences in responsiveness of ESSDAI between rituximab and placebo groups were found. These results support the notion that the recently developed ESSDAI is a sensitive instrument to assess changes in disease activity over time. Apparently, ESSDAI at week 24 is a good endpoint to assess treatment efficacy of rituximab.

In **chapter 6** the results of an open-label study with abatacept, the Active Sjögren Abatacept Pilot (ASAP) study are presented. Abatacept is a fully human, fusion molecule of IgG-Fc and cytotoxic T-lymphocyte antigen 4 (CTLA-4) that modulates CD28-mediated T-cell co-stimulation. Co-stimulation between antigen-presenting cells and T-cells, and between B-cells and T-cells is an essential step in T-cell-dependent immune responses including autoimmune responses.[9] In the ASAP study the efficacy and safety of abata-

cept was assessed in 15 patients with early and active pSS. Disease activity (assessed with ESSDAI and ESSPRI), rheumatoid factor (RF) and IgG levels decreased significantly during abatacept treatment and increased post-treatment. Fatigue and HR-QoL improved significantly during treatment. Salivary and lacrimal gland function did not change during treatment. No serious side effects or infections occurred. In conclusion, in this open-label proof of concept study, abatacept treatment was shown to be effective, safe and well tolerated in pSS patients.

GENERAL DISCUSSION

Is there a need to treat Sjögren's syndrome?

SS is known to affect patient's physical, psychological and social functioning,[10] but the impact of SS on HR-QoL and especially on employment and disability is less well studied. Such information is needed to interpret the burden of disease and to gain insight into the necessity for treatment of pSS. The analysis described in **chapter 2** was performed to gather this information. Like other systemic autoimmune diseases, SS has indeed a substantial impact on patients' HR-QoL, employment and disability as reflected by lower SF-36 scores and employment rates, and higher disability rates compared with the general Dutch population. A recent study in the United Kingdom in 639 pSS patients confirmed our results regarding the high impact of pSS on HR-QoL.[11] The high prevalence of SS along with the high impact on HR-QoL, employment and disability described in **chapter 2** justifies further research on the intervention with biological therapy in SS, even though these treatments are expensive and intensive. At present, no curative or causal treatment exists for SS. The classic therapeutic approach is based on symptomatic treatment of glandular manifestations and broad-spectrum immunosuppression directed against organ specific systemic disease (**chapter 3**).[2] SS research focusing on the development of more effective targeted therapies that selectively target different pathogenic pathways and that reduce disease activity and/or prevents disease progression is therefore warranted. Furthermore, validation of the recently developed tools (a.o., ESSDAI and ESSPRI) for rating disease activity and for assessing efficacy of intervention therapy is needed.

How to evaluate disease activity and treatment effect in Sjögren's syndrome?

The heterogeneous nature SS and its variable course has made it difficult to quantify the extent and severity of the disease in individual patients. Furthermore, the common drawback of the studies evaluating the efficacy of (biological) therapy in pSS reported yet is the large variety of outcome parameters used in the various studies. This variation makes comparison of results between studies difficult if even possible. It is therefore crucial to have access to a reliable set of assessments by which the efficacy of a particular therapy can be evaluated, meanwhile allowing evidence-based comparison of

the various treatment approaches in pSS.[12] Reliable outcome assessments are amongst others needed for salivary and lacrimal gland function, serological parameters, HR-QoL, fatigue, cost-effectiveness and cost-utility and, in particular, disease activity (see table 1).

Salivary gland related parameters

Within the wide spectrum of clinical manifestations of SS, salivary gland function is considered a key manifestation.[13] Salivary gland parameters are particularly thought to be of value in diagnosing SS and assessing progression of SS. Its value for treatment evaluation might be limited or only of clinical value in a subgroup of SS patients due to the level of glandular damage that is present at the time a certain treatment is started.

Dysfunction of the salivary glands results in changes in the amount and composition of saliva. Saliva is considered an attractive diagnostic fluid because saliva has several key advantages, including noninvasiveness, ease of sample collection and low costs. Therefore, sialometry and sialochemistry can be used as assessment tools either by collecting whole saliva (the combined secretions of all salivary glands) or by collecting glandular saliva (gland-specific saliva).[12] Although unstimulated whole salivary flow rate is a major diagnostic criterion for salivary gland dysfunction in SS,[14] whole saliva is probably of less a value when aiming for scoring the progression of SS. At the time SS develops not all major salivary glands may already show (severe) dysfunction (in many patients submandibular salivary glands are more severely affected in an earlier stage than parotid glands).[15] By using glandular saliva, patients with SS may be diagnosed at an earlier stage, and disease progression can be evaluated in a noninvasive way. With regard to early salivary diagnostics in general clinical practice, whole saliva might be preferred as it may contain a wide array of informative proteins, partly originating from serum components that leak into whole saliva. These proteins can be used as biomarkers.[16-20] Recent progress in proteomics and genomics has shown that a panel of salivary proteins present in whole saliva can discriminate pSS patients from both SLE patients and healthy controls.[17] Furthermore, Hu et al[20] demonstrated the potential of a high-throughput protein microarray approach for the discovery of autoantibody biomarkers. Further validation of these biomarkers may lead to a clinical tool for simple, noninvasive detection of pSS at low cost. Such a study (NCT01807689) is currently underway supported by a grant from the National Institutes of Health.

Salivary gland ultrasound is another upcoming diagnostic tool in SS to be applied in clinical practice. Although not currently included in the American-European Consensus Group (AECG) and the American College of Rheumatology (ACR) classification criteria for SS,[14,21] ultrasonography is increasingly being used in clinical practice and may be added to the SS criteria in the future, most likely replacing scintigraphy and/or sialography.[22,23] The use of ultrasound requires standardisation and validation before it can be considered as a tool to be commonly applied for diagnosis and classification of SS.

Histologic analysis of salivary gland tissue is a widely accepted diagnostic tool in SS.

Table 1. Evaluation of disease activity and treatment effect in SS.

PRIMARY ENDPOINTS		
Disease activity • ESSDAI • ESSPRI		
SECUNDARY ENDPOINTS		
Salivary gland objective • SWS • UWS • Gland specific saliva • Ultrasound • Salivary gland biopsy	**Lacrimal gland objective** • Schirmer's test • Tear break-up time • Lissamin green test • OSS	**Serological** • IgG, RF • Complement • Cryoglobulins • B- and T-cell counts • Others
HR-QoL • SF-36 • EQ-5D • Others	**Fatigue** • MFI • VAS fatigue • Others	**Cost-effectiveness / cost-utility** • Quality adjusted life years

ESSDAI, EULAR Sjögren's syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's syndrome Patient Reported Index, SWS, stimulated whole salivary flow rate; UWS, unstimulated whole salivary flow rate; OSS, ocular staining score; IgG, Immunoglobulin G; RF, rheumatoid factor; SF-36, short form-36 health survey; EQ-5D, EuroQoL-5 dimension; MFI, Multidimensional Fatigue Index; VAS, Visual Analogue Scale.

Although labial salivary gland biopsies are a main criterion in both the AECG[14] and ACR[21] classification criteria sets, studies comparing labial and parotid gland biopsies have shown that the diagnostic power of parotid gland biopsies was at least comparable to that of labial gland biopsies in the diagnostic workup of SS according to the AECG criteria.[24-26] Furthermore, salivary gland biopsies are an asset in the evaluation of the efficacy of intervention therapy with biological DMARDs.[27-29] In this respect, parotid gland biopsies have advantages over labial biopsies, mainly because a parotid gland can be biopsied more often and saliva samples can be obtained from the same gland. It has to be assessed whether ultrasonography of the salivary glands is complementary to, or can replace parotid gland biopsies for diagnostic purposes.

Lacrimal gland related parameters

Procedures for evaluating the ocular component of SS include sequenced unanaesthetised Schirmer's test, tear break-up time, ocular surface staining and external eye examination at the slit lamp. Recently, the Sjögren's International Collaborative Clinical Alliance (SICCA) introduced the SICCA ocular staining score (OSS), which evaluates conjunctival and corneal damage due to keratoconjunctivitis.[30] The OSS is used for diagnosing the ocular component of SS in the ACR classification criteria.[21] The tech-

nique involves fluorescein staining of the cornea and lissamine green staining of the interpalpebral conjunctiva to calculate an OSS. The OSS may have a value ranging from 0 (no corneal or conjunctival staining detected) to 12 for each eye. OSS scores ≥3 are considered abnormal and represent keratoconjunctivitis sicca. Whitcher et al[30] found strong associations between abnormal OSS, positive serologic results, and positive labial salivary gland focus scores ($p<0.0001$) among 1208 participants of the SICCA cohort. However, the current cut-off value for the OSS is doubted by the EULAR/ACR working group who currently tries to intergrate the AECG and ACR criteria. Probably, the OSS score will be set at a higher level in the future AECG/ACR criteria. Furthermore, it still has to be shown how applicable the OSS score is for Sjögren's diagnostics in routine clinical practice as a trained, calibrated ophthalmologist is needed in contrast to, e.g., the Schirmer's test that is commonly used in current routine clinical practice by, e.g., rheumatologists too.

Serological parameters

Serological parameters such as autoantibodies and immunoglobulin levels are valuable in diagnosing SS and assessing progression of SS. Jonsson et al[31] showed in a study involving 44 pSS patients that two thirds of them had detectable autoantibodies years before symptom onset (primarily antinuclear antigens (ANA), followed by RF, anti-Ro60/SSA, anti-Ro52/SSA, and anti-La/SSB). Autoantibody profiling may therefore identify individuals at risk many years before disease onset. The significance of these presymptomatic autoantibodies for determining prognosis and treatment remains to be determined. Furthermore, once diagnosed with SS, identifying serological markers of severity for SS could be very helpful in the evaluation and management of these patients. Low C3 and C4 levels, cryoglobulins, monoclonal paraproteinaemia, anti-Ro/SSA, anti-La/SSB, RF and hypergammaglobulinaemia represent poor prognostic serological features in pSS and may be indicative for patients at risk of extraglandular manifestations and lymphomas.[32-39] The value of serum analysis is further supported by its use in the evaluation of the effect of treatment with biological DMARDs. The decrease and re-increase in RF, IgG and ß2-microgloblin following treatment with rituximab in pSS patients might be a useful serum parameter for treatment effects (see **chapter 4.1**).[40] The same pattern for RF and IgG levels is seen after treatment with abatacept (**chapter 6**).

Identification of other clinically applicable disease-related biomarkers could also contribute to diagnosis of SS, to measure disease activity and to identify subcategories of patients.[41] Analysis of changes in immune activation markers, such as cytokines involved in lymphocyte activation and inflammation, following rituximab treatment might be indicative for response to treatment and, possibly for recurrence of disease activity.[42] Recently, Maria and coworkers[43] showed that Myxovirus-resistance protein I (MxA) might be useful as a biomarker for interferon (IFN) type I bioactivity in pSS patients. Increased MxA levels are associated with features of active disease such as higher ESSDAI scores,

and elevated levels of immunoglobulins (IgG, IgA and IgM) and autoantibodies (RF, anti-Ro/SSA and anti-La/SSB). Whether MxA-positivity or negativity defines subgroups of pSS patients with different prognostic outcomes is currently not clear. Furthermore, long-term longitudinal follow-up validation studies are required to investigate the role of MxA as clinically applicable biomarker for disease activity.[41] In RA patients, the IFN type I signature is predictive for non-responsiveness to anti-CD20 therapy with rituximab.[44] In the future, the IFN type I signature as defined by MxA might be used to select pSS patients that may benefit from rituximab treatment, or other biological DMARDs.[41]

HR-QoL and fatigue instruments

As shown in **chapter 2**, HR-QoL (assessed with SF-36) is significantly reduced in SS patients. Fatigue was an important predictor for explanatory variable for reduced physical and mental HR-QoL. Forty percent of SS patients ranked fatigue as their most severe symptom. The high impact of having pSS on HR-QoL (assessed with EuroQoL-5 dimension (EQ-5D)) was recently confirmed in 639 pSS patients in the UK, with pain and depression being the most important predictors, whereas the relative contribution of fatigue was smaller in this study.[11] As is for HR-QoL, the subjective experience of fatigue is primarily evaluated by structured questionnaires too, which often include items related to possible causes and consequences of fatigue in every day life.[45] pSS patients show high ratings on such questionnaires.[46-48] HR-QoL and fatigue are therefore important treatment targets in SS.

Generic assessment tools such as SF-36 and EQ-5D for HR-QoL and multidimensional fatigue inventory (MFI) for fatigue do, however, not reflect outcomes specific to a specific condition such as pSS. Therefore, there is a continuing debate about the use of generic versus condition-specific tools for measures. The relative contribution of disease specific symptoms such as dryness or fatigue to HR-QoL may not be captured by generic measures for HR-QoL. Furthermore, predictors do not necessarily equate to causative factors. E.g., condition specific measures reflect the outcomes of interest to the patients concerned whereas generic measures may not.

An important asset of generic instruments such as SF-36 and EQ-5D, on the other hand, is that they allow data to be compared across diseases, and can be used for cost-utility assessments in future trials (see below).[11] Therefore, also after pSS specific tools for HR-QoL and fatigue have become available; it is advised to continue the use of commonly applied generic tools for HR-QoL and fatigue in trials for evaluating pSS to make comparison with previous studies possible.

Cost-effectiveness and cost-utility

New therapeutic approaches, e.g., rituximab and abatacept, must demonstrate their efficacy and safety in SS patients to be approved for clinical use before they become part of treatment of SS beyond research settings. However, healthcare costs are rising

and budgets are limited which may hesitate insurance companies to reimburse such treatments. Therefore, assessing the cost-effectiveness of (new) treatments becomes increasingly important. Cost-effectiveness analyses and cost-utility analyses (a specific type of cost-effectiveness analysis) are common methods for assessing the costs and health benefits of an intervention.[49] Costs refer to the total net expenditures related to an intervention, including the costs of treatment, adverse treatment effects, and future possible savings from the prevention of disease or morbidity. Cost-utility analysis frequently uses quality-adjusted life years gained to reflect both prolongation of life and the HR-QoL associated with those years.[50,51] In future trials in pSS, cost-effectiveness and cost-utility of (biological) therapeutic agents should be addressed too.

Disease activity indices

As mentioned before, in the past years many attempts have been made to develop valid tools to assess patients' symptoms as dryness, fatigue and musculoskeletal pain as well as to assess systemic manifestations like arthritis, cutaneous manifestations and glomerulonephritis.[52] In 2010, an international project supported by the EULAR proposed the ESSDAI and the ESSPRI as disease activity indices.[3,4] The ESSDAI evaluates systemic complications, salivary gland enlargement and B-cell biomarkers, whereas ESSPRI was designed to assess patient's symptoms. Because ESSDAI and ESSPRI give a complete picture of pSS, the widespread use of these indices can support the rating of disease activity in SS as well as be an important asset in assessing the efficacy of symptomatic or intervention treatment. Therefore, using ESSDAI and ESSPRI as primary endpoints in a study seems a rational approach.

ESSDAI and ESSPRI have been recently validated in a prospective international cohort of 395 pSS patients.[53] Furthermore, the ability of ESSDAI and ESSPRI to detect changes after biological therapy has been confirmed in a number of open-label and RCTs (see **chapters 5.1**, **5.2** and **6**).[51] In these trials, it was shown that a certain treatment was effective as ESSDAI and ESSPRI improved significantly after treatment. Based on these promising results, ESSDAI is currently considered to be the preferred scoring system for disease activity and ESSPRI is used when primarily aiming for the experience of patients with a certain treatment. ESSDAI is increasingly used in clinical and biological studies aiming for assessments of new biomarkers of disease activity or risk factors for the development of lymphoma.[52,54,55] ESSDAI correlates with B-cell biomarkers such as BAFF,[56] ß2 microglobulin and serum free light chains of immunoglobulins.[57,58] ESSPRI is also broadly used and correlates with HR-QoL measures[59] and functional status,[60] and was shown as a predictor of the health status of pSS patients.[61] Seror and coworkers[62] recently estimated the minimum clinically important improvement (MCII) of ESSDAI. Based on recent trial data, they proposed to use the threshold of moderate activity as entry criteria (patients with ESSDAI $\geq$5), and to define response to treatment as a significant improvement of ESSDAI (at least 3 points). The MCII of ESSPRI is not yet available.

Which treatment for SS is yet available?

It is presumed that early, accurate diagnosis of SS may prevent or ensure adequate treatment of symptoms and systemic complications of SS.[63] Because patients have concomitant oral, ocular and systemic medical problems, the management of the patient with SS should ideally involve a multidisciplinary team of health care practitioners with good lines of communication between them. In a multidisciplinary team with a specialised rheumatologist, oral and maxillofacial surgeon, ophthalmologist, pathologist, haematologist, dentist and oral hygienist, SS patients can get the care they need (**chapter 3**).

The inventory of the management of both glandular and extraglandular manifestations of SS (**chapter 3**) revealed that sicca manifestations are usually treated symptomatically through preventive measures, stimulation of residual glandular function, and/or administration of topical therapies, such as saliva substitutes and artificial tears. E.g., stimulation salivary flow with secretagogues is the treatment of choice in patients with residual salivary gland function. The management of extraglandular features must be tailored to the specific organ or organs involved. Limited data have been obtained from RCTs in pSS, however. As a result, the treatment of systemic symptoms using therapies including traditional and biological DMARDs is yet still mainly empirical.

Biological DMARDs that target molecules and receptors involved in the pathogenesis of SS are considered to be promising therapies. Several biological DMARDs have been evaluated in RCTs in pSS, but not all agents studied were effective. RCTs failed to show clinical effect of anti-TNF and IFN-α in pSS, however, B-cell depleting therapy with e.g., rituximab (**chapter 4**) and epratuzumab,[64] modulating costimulation with e.g., abatacept (**chapter 6**) and targeting BAFF with e.g., belimumab[51] look promising. Other potential targets for biological (combination) treatment include cytokines such as IL-1 and IL-6, adhesion molecules and chemokines such as CXCL10 and CXCL13.

What about rituximab and abatacept?

Open-label studies and RCTs (see **chapter 4 and chapter 5.2**) showed efficacy of rituximab in improving, amongst others, disease activity (ESSDAI), patients' symptoms (ESSPRI), extraglandular manifestations, HR-QoL, fatigue, and salivary flow. With regard to salivary flow, a beneficial effect was mainly observed in subjects with residual function of the glands. Retreatment with rituximab (**chapter 4.2 and 5.1**) resulted in comparable beneficial effects, as initial treatment on objective parameters, including ESSDAI. In the open-label Active Sjögren Abatacept Pilot (ASAP; **chapter 6**), abatacept treatment was also shown effective and safe in a group of 15 patients with early and active pSS too. During treatment with abatacept, disease activity assessed with ESSDAI, ESSPRI and physicians' GDA decreased, RF and IgG levels dropped, fatigue diminished and patients experienced improved HR-QoL. Salivary and lacrimal gland function did not change during treatment (**chapter 6**) or showed a slight, but clinically irrelevant, improvement in the study with abatacept in pSS patients by Adler et al.[27]

In the literature, some SS experts suggest to limit biological therapy for pSS patients with severe extraglandular manifestations,[39,65] because the long term (side-) effects of treatment with biological agents are not known yet. SS patients with (severe) extraglandular manifestations indeed benefit significantly from (re)treatment with rituximab.[66] However, the results of our RCT with rituximab and the ASAP study indicate that although pSS patients with early disease might not have severe extraglandular manifestations such as glomerulonephritis or pulmonary involvement, the majority of these patients (70-80%) had active disease as reflected by ESSDAI scores ≥5 at baseline. These observations are in line with the study by Carubbi and co-workers[28] who showed in comparative study in 41 pSS patients with early and active disease (ESSDAI ≥6) that rituximab treatment resulted in a faster and more pronounced decrease of ESSDAI and other clinical parameters compared with traditional DMARDs. Thus, to our opinion, patients with early and active disease, as reflected by higher ESSDAI scores, probably ≥5 at baseline[62] (most likely patients with at least high levels of IgG and RF, increasing complaints of fatigue and/or sicca complaints and/or swelling of the parotid gland) are the preferred patients to be treated with biological therapy, as well as patients with severe extraglandular manifestations. pSS patients with ESSDAI scores ≥5 are not patients with just sicca complaints, but pSS patients with other manifestations related to pSS too.

Response rates based on ESSDAI for rituximab (**chapter 4.1**) and abatacept (**chapter 6**) were comparable at week 24 for rituximab and abatacept, namely 77% and 86%, respectively, whereas response was 17% for the placebo group from the RCT with rituximab (**chapter 4.1**). Response rate is clearly higher in treated patients. Response was defined as a decrease in ESSDAI ≥3 in patients with an ESSDAI baseline score ≥5.[53] In RA, a meta-analysis comparing efficacy of several biological DMARDs also showed similar efficacy profiles for abatacept and rituximab.[67] One should however keep in mind, that the studies presented in this thesis were not designed for direct comparison, e.g.,median ESSDAI is higher in the ASAP study population 11 ((range 2-21); **chapter 6**) versus 8 ((range 4-13); **chapter 4.1**) than in the rituximab study. Furthermore, relatively more males were included in the ASAP study. Unfortunately, numbers of patients are too small to perform yet a subanalysis to identify predictive variables for response, giving information on which patients will respond and benefit from which treatment.

Regarding safety, (serious) adverse events and infection results were not registered uniformly, in the various studies yet published. This omission does not allow for direct comparison between our studies, even with regard to our studies with rituximab and abatacept. In general, in the RCT with rituximab, the incidence of infusion reactions and infections reported for the rituximab group was largely comparable to that of the placebo group. In the ASAP study, no serious infections, opportunistic infections or atypical presentation of infections occurred and none of the infections required hospitalisation, which is comparable to safety results found in RA patients treated with abatacept.[68,69] The apparent high proportion of upper airway infections is most likely a result of the way

infections and infestations were collected; self-reported by the patients. Most patients did not visit a doctor for these probable (but not proven) infections, and it is not clear whether these self-reported infections were related to the use of abatacept or were normal features that may occur in pSS (there was no placebo group). Whether this explanation holds, needs to be investigated in a RCT.

An important disadvantage specific to the treatment with biological DMARDs that are raised in animals, like rituximab which origin is chimeric, is the hazard of developing serum sickness or serum sickness-like disease. Although concomitant use of steroids reduces the risk of developing these adverse events, they may still occur. These unwanted adverse events might be prevented by the use of fully humane antibodies. The currently available humane antibodies (a.o., abatacept) are promising but need further study. Thus, abatacept is presumed to have a more favorable safety profile than chimeric DMARDs such as rituximab. In RA patients, in an observational study fewer serious infections were found with abatacept than with rituximab.[70] It should, however, be mentioned that in this study the contribution of demographics, comorbidities and steroid use contributed to a substantially greater variability to infection risk directly related to the studied biological DMARDs. Unfortunately, also in RA no head to head comparison is available for these biological agents. In pSS, larger RCTs for these agents are needed and ideally a comparative study should be done before any conclusion can be drawn.

Which (re)treatment schedule should be followed for rituximab treatment?

Thusfar the largest number of clinical trials investigating the efficacy of biological agents in patients with SS involved rituximab. Given the promising results of these trials, for rituximab the most optimal (re)treatment schedule can be proposed. Additional studies with abatacept are needed before the optimal (re)treatment schedule for abatacept can be worked out.

As is clear from the trials published this far, the effect of rituximab treatment is transient and treated patients usually experience relapse of the disease. This relapse parallels the return of B-cells in peripheral blood. Although the duration of a beneficial treatment effect differed between trials, a beneficial effect it is usually seen up to 24 or 36 weeks after treatment. The patients in our study (**chapter 4.2**) that were retreated with rituximab responded well and reported a beneficial effect comparable to that of the initial treatment with rituximab. Recently, Gottenberg et al[66] found good physician-reported efficacy and tolerance during repeated courses of rituximab in 41 initially responding pSS patients.

In RA, repeated courses of rituximab were shown to be very effective in previously responsive RA patients and a second course of rituximab could even result in a positive response in some of the RA patients with partial or no response to initial treatment. Treatment with rituximab every 6 months showed better clinical efficacy than on-demand treatment in RA, with no significantly increased adverse events.[71] Given the

positive effect of retreatment in pSS and the knowledge about retreatment in RA, offering patients maintenance therapy with rituximab infusions every 6 months may be a reasonable approach. Advantages of maintenance therapy might be a reduction or even arrest of disease progression and a better HR-QoL for a longer period. This concept was recently supported by the study of Carubbi and coworkers.[28] Forty-one patients with early and active pSS (ESSDAI $\geq$6) were followed for a 120 weeks period. They were either treated with 6 courses of rituximab (a course consisted of 2 infusions of 1,000 mg rituximab in combination with prednisolon, a course was repeated every 24 weeks for a 120 weeks period) or with traditional DMARDs (hydroxychloroquine, methotrexate, cyclosporine, in combination with prednisolon). In this study, ESSDAI significantly decreased compared with baseline, starting from week 24 in both groups. However, a significantly stronger reduction in ESSDAI was found in the rituximab group from week 24, and this effect was observed throughout the whole study period. A similar pattern was found for Visual Analogue Scale (VAS) pain and General Disease Activity (GDA) score. VAS dryness, VAS fatigue, unstimulated whole salivary flow rate and Schirmer's test were not affected in the traditional DMARD group, but showed a significant improvement in the rituximab treated patients. These data confirm that pSS patients with early and active disease are likely to benefit from rituximab infusions (e.g., 1000 mg twice with an interval of 2 weeks) every 24 weeks in combination with steroids.

Is it beneficial to combine biological therapies?

Thusfar, there is a lack of long-term data to allow for reliable statements on efficacy and safety of rituximab, abatacept and belimumab 'monotherapy' in pSS. Large(r) RCTs with these biological DMARDs in pSS patients with long-term follow-up are needed, before combining of, e.g., rituximab with other biological therapies can even be considered as an adjuvant therapy. Theoretically, combining rituximab with other biologicals is presumed to be beneficial, e.g., a combination therapy that targets CD20 (e.g., rituximab) and BAFF (e.g., belimumab): B-cells play a major role in orchestrating the pathological immune response in pSS and BAFF is a strong stimulant for B-cell activation and proliferation and for B-cell survival. Support for this proposed combination therapy comes from the observed increase in serum levels of BAFF following rituximab treatment.[72] Furthermore, Pers et al[73] showed that higher baseline serum levels of BAFF in pSS patients resulted in a shorter duration of B-cell depletion by rituximab. These observations presume that there is a role of BAFF in the repopulation of B-cells after rituximab treatment. A combination therapy targeting CD20 and BAFF may therefore delay B-cell repopulation (with auto-reactive cells) and re-emergence of clinical symptoms. Another possibility could be targeting co-stimulation (e.g., abatacept) at some time point after rituximab treatment, but before the reappearance of B-cells in the blood! Such an approach might prevent the activation of autoreactive B-cells that either escaped rituximab treatment or were newly generated.

Future perspectives

Understanding of the pathogenetic mechanisms underlying pSS is rapidly expanding. This growing knowledge helps to establish known and novel biomarkers for early diagnosis of SS, to measure disease activity and disease progression in SS patients, and to define subgroups of pSS patients that are presumed to be susceptible to a particular treatment.[74] Such knowledge will focus in what (sub)group of pSS the many biological DMARDs that are currently available or in development preferably have to be tested, either as a sole or combination treatment. With regard to agents that have proven effective and safe in small pSS studies (e.g., rituximab, epratuzumab, abatacept and belimumab), large(r) RCTs are warranted to assess the long-term effects of these treatments, to assess which treatment schedule should be followed for each biological DMARD, and to select SS patients in whom a particular treatment is thought most effective. The result of ongoing trials with newly introduced biological agents in pSS such as tocilizumab (humanised monoclonal antibody against IL-6 receptor), anakinra (IL-1 receptor antagonist) and baminercept (lymphotoxin ß receptor IgG1) are awaited (www.clinicaltrials.gov). In addition, synthetic DMARDs that inhibit B-cell receptor signaling molecules and cytokine receptors have become available.[74]

Besides better understanding the pathogenetic process and the availability of traditional and biological DMARDs, assessment of disease activity in pSS is an essential step to rate efficacy of the treatment. With the development and validation of the ESSDAI and ESSPRI, important tools have become available for rating systemic manifestations and patients' symptoms. In the past, lack of response criteria has set an evidence based comparison of different treatments tested in pSS aside. Similarly, the lack of a uniform classification system for SS makes comparison of treatment effects between studies difficult. Therefore, merging the AECG and ACR criteria to 1 classification system to be used in all studies in SS patients is eagerly awaited.

References

1 Fox RI. Sjögren's syndrome. Lancet 2005;366:321-31.

2 Ramos-Casals M, Brito-Zeron P, Siso-Almirall A, et al. Topical and systemic medications for the treatment of primary Sjögren's syndrome. Nat Rev Rheumatol 2012;8:399-411.

3 Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

4 Seror R, Ravaud P, Mariette X, et al. EULAR Sjögren's syndrome patient reported index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. Ann Rheum Dis 2011;70:968-72.

5 Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface molecule B1 is functionally linked with B cell activation and differentiation. J Immunol 1985;135:973-9.

6 Tedder TF, Forsgren A, Boyd AW, et al. Antibodies reactive with the B1 molecule inhibit cell cycle progression but not activation of human B lymphocytes. Eur J Immunol 1986;16:881-7.

7 Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest 2010;120:214-22.

8 Mabthera [Roche]. Product information, version of 20th of November 2013.

9 Reiser H, Stadecker MJ. Costimulatory B7 molecules in the pathogenesis of infectious and autoimmune diseases. N Engl J Med 1996;335:1369-77.

10 Bjerrum K, Prause JU. Primary Sjögren's syndrome: a subjective description of the disease. Clin Exp Rheumatol 1990;8:283-8.

11 Lendrem D, Mitchell S, McMeekin P, et al. Health-related utility values of patients with primary Sjögren's syndrome and its predictors. Ann Rheum Dis 2013 [Epub a head of print].

12 Vissink A, Bootsma H, Kroese FG, et al. How to assess treatment efficacy in Sjögren's syndrome? Curr Opin Rheumatol 2012;24:281-9.

13 Mignogna MD, Fedele S, Lo Russo L, et al. Sjögren's syndrome: the diagnostic potential of early oral manifestations preceding hyposalivation/xerostomia. J Oral Pathol Med 2005;34:1-6.

14 Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European consensus group. Ann Rheum Dis 2002;61:554-8.

15 Pijpe J, Kalk WW, Bootsma H, et al. Progression of salivary gland dysfunction in patients with Sjögren's syndrome. Ann Rheum Dis 2007;66:107-12.

16 Ferraccioli G, De Santis M, Peluso G, et al. Proteomic approaches to Sjögren's syndrome: a clue to interpret the pathophysiology and organ involvement of the disease. Autoimmun Rev 2010;9:622-6.

17 Hu S, Gao K, Pollard R, et al. Preclinical validation of salivary biomarkers for primary Sjögren's syndrome. Arthritis Care Res (Hoboken) 2010;62:1633-8.

18 Ryu OH, Atkinson JC, Hoehn GT, et al. Identification of parotid salivary biomarkers in Sjögren's syndrome by surface-enhanced laser desorption/ionization time-of-flight mass spectrometry and two-dimensional difference gel electrophoresis. Rheumatology (Oxford) 2006;45:1077-86.

19 Hu S, Wang J, Meijer J, et al. Salivary proteomic and genomic biomarkers for primary Sjögren's syndrome. Arthritis Rheum 2007;56:3588-600.

20 Hu S, Vissink A, Arellano M, et al. Identification of autoantibody biomarkers for primary Sjögren's syndrome using protein microarrays. Proteomics 2011;11:1499-507.

21 Shiboski SC, Shiboski CH, Criswell L, et al. American college of rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's international collaborative clinical alliance cohort. Arthritis Care Res (Hoboken) 2012;64:475-87.

22 Bootsma H, Spijkervet FK, Kroese FG, et al. Toward new classification criteria for Sjögren's syndrome? Arthritis Rheum 2013;65:21-3.

23 Bowman SJ, Fox RI. Classification criteria for Sjögren's syndrome: nothing ever stands still! Ann Rheum Dis 2014;73:1-2.

23 Wise CM, Agudelo CA, Semble EL, et al. Comparison of parotid and minor salivary gland biopsy specimens in the diagnosis of Sjögren's syndrome. Arthritis Rheum 1988;31:662-6.

24 Marx RE, Hartman KS, Rethman KV. A prospective study comparing incisional labial to incisional parotid biopsies in the detection and confirmation of sarcoidosis, Sjögren's disease, sialosis and lymphoma. J Rheumatol 1988;15:621-9.

25 Pijpe J, Kalk WW, van der Wal JE, et al. Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. Rheumatology (Oxford) 2007;46:335-41.

26 Pijpe J, Meijer JM, Bootsma H, et al. Clinical and histologic evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjögren's syndrome. Arthritis Rheum 2009;60:3251-6.

27 Adler S, Korner M, Forger F, et al. Evaluation of histological, serological and clinical changes in response to abatacept treatment of primary Sjögren's syndrome: a pilot study. Arthritis Care Res (Hoboken) 2013 [Epub a head of print].

28 Carubbi F, Cipriani P, Marrelli A, et al. Efficacy and safety of rituximab treatment in early primary Sjögren's syndrome: a prospective, multi-center, follow-up study. Arthritis Res Ther 2013;15:R172.

29 Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's syndrome international registry. Am J Ophthalmol 2010;149:405-15.

30 Jonsson R, Theander E, Sjostrom B, et al. Autoantibodies present before symptom onset in primary Sjögren syndrome. JAMA 2013;310:1854-5.

31 Baimpa E, Dahabreh IJ, Voulgarelis M, et al. Hematologic manifestations and predictors of lymphoma development in primary Sjögren syndrome: clinical and pathophysiologic aspects. Medicine (Baltimore) 2009;88:284-93.

32 Brito-Zeron P, Ramos-Casals M, Nardi N, et al. Circulating monoclonal immunoglobulins in sjogren syndrome: prevalence and clinical significance in 237 patients. Medicine (Baltimore) 2005 Mar;84(2):90-7.

33 Voulgarelis M, Skopouli FN. Clinical, immunologic, and molecular factors predicting lymphoma development in Sjögren's syndrome patients. Clin Rev Allergy Immunol 2007;32:265-74.

34 Baldini C, Pepe P, Quartuccio L, et al. Primary Sjögren's syndrome as a multi-organ disease: impact of the serological profile on the clinical presentation of the disease in a large cohort of Italian patients. Rheumatology (Oxford) 2013 [Epub a head of print].

35 Skopouli FN, Dafni U, Ioannidis JP, et al. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. Semin Arthritis Rheum 2000;29:296-304.

36 Theander E, Henriksson G, Ljungberg O, et al. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006;65:796-803.

37 Garcia-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjögren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. Medicine (Baltimore) 2002;81:270-80.

38 Solans-Laque R, Lopez-Hernandez A, Bosch-Gil JA, et al. Risk, predictors, and clinical characteristics of lymphoma development in primary Sjögren's syndrome. Semin Arthritis Rheum 2011;41:415-23.

39 Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjögren's syndrome. Ann Rheum Dis 2007;66:351-7.

40 Kroese FG, Bootsma H. Biomarkers: new biomarker for Sjögren's syndrome--time to treat patients. Nat Rev Rheumatol 2013;9:570-2.

41 Pollard RP, Abdulahad WH, Bootsma H, et al. Predominantly proinflammatory cytokines decrease after B cell depletion therapy in patients with primary Sjögren's syndrome. Ann Rheum Dis 2013;72:2048-50.

42 Maria NI, Brkic Z, Waris M, et al. MxA as a clinically applicable biomarker for identifying systemic interferon type I in primary Sjögren's syndrome. Ann Rheum Dis 2013 [Epub a head of print].

43 Raterman HG, Vosslamber S, de Ridder S, et al. The interferon type I signature towards prediction of non-response to rituximab in rheumatoid arthritis patients. Arthritis Res Ther 2012;14:R95.

44 Mengshoel AM, Norheim KB, Omdal R. Primary Sjögren's syndrome - fatigue is an ever-present, fluctuating and uncontrollable lack of energy. Arthritis Care Res (Hoboken) 2013 [Epub a head of print].

45 Theander L, Strombeck B, Mandl T, et al. Sleepiness or fatigue? Can we detect treatable causes of tiredness in primary Sjögren's syndrome? Rheumatology (Oxford) 2010;49:1177-83.

46 Lwin CT, Bishay M, Platts RG, et al. The assessment of fatigue in primary Sjögren's syndrome. Scand J Rheumatol 2003;32:33-7.

47 Barendregt PJ, Visser MR, Smets EM, et al. Fatigue in primary Sjögren's syndrome. Ann Rheum Dis 1998;57:291-5.

48 Weinstein MC, Stason WB. Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 1977;296:716-21.

49 Provenzale D, Lipscomb J. Cost-effectiveness: definitions and use in the gastroenterology literature. Am J Gastroenterol 1996;91:1488-93.

50 Eisenberg JM. Clinical economics. A guide to the economic analysis of clinical practices. JAMA 1989;262:2879-86.

51 Mariette X, Seror R, Quartuccio L, et al. Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis 2013 [Epub a head of print].

52 Seror R, Theander E, Bootsma H, et al. Outcome measures for primary Sjögren's syndrome: ready for use? [Submitted].

53 Seror R, Theander E, Brun JG, et al. Validation of EULAR primary Sjögren's syndrome disease activity and patient indexes. Arthritis Rheum 2013;64:S1078.

54 Theander E, Vasaitis L, Baecklund E, et al. Lymphoid organisation in labial salivary gland biopsies is a possible predictor for the development of malignant lymphoma in primary Sjögren's syndrome. Ann Rheum Dis 2011;70:1363-8.

55 Tobon GJ, Saraux A, Gottenberg JE, et al. Role of fms-like tyrosine kinase 3 ligand as a potential biologic marker of lymphoma in primary Sjögren's syndrome. Arthritis Rheum 2013;65:3218-27.

56 Quartuccio L, Salvin S, Fabris M, et al. BLyS upregulation in Sjögren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal expansion in the salivary glands. Rheumatology (Oxford) 2013;52:276-81.

57 Pertovaara M, Korpela M. Serum ß2 microglobulin correlates with the new ESSDAI in patients with Sjögren's syndrome. Ann Rheum Dis 2011;70:2236-7.

58 Gottenberg JE, Seror R, Miceli-Richard C, et al. Serum levels of ß2-microglobulin and free light chains of immunoglobulins are associated with systemic disease activity in primary Sjögren's syndrome. Data at enrollment in the prospective ASSESS cohort. PLoS One 2013;8:e59868.

59 Cho HJ, Yoo JJ, Yun CY, et al. The EULAR Sjögren's syndrome patient reported index as an independent determinant of health-related quality of life in primary Sjögren's syndrome patients: in comparison with non-Sjögren sicca patients. Rheumatology (Oxford) 2013;52:2208-17.

60 Hackett KL, Newton JL, Frith J, et al. Impaired functional status in primary Sjögren's syndrome. Arthritis Care Res (Hoboken) 2012;64:1760-4.

61 Ng WF, Mitchell S, Lendrem D, et al. How good are the EULAR sjögren's syndrome disease activity index (ESSDAI), and eular sjögren's syndrome patients reported index (ESSPRI) in predicting health status in primary sjögren's syndrome? Ann Rheum Dis 2012;71:553.

62 Seror R, Gottenberg JE, Bootsma H, et al. Defining disease activity rates and minimal clinically important improvement (MCII) with the EULAR Sjögren's syndrome disease activity index (ESSDAI). [Abstract submitted to EULAR 2014].

63 Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren's syndrome. Arch Intern Med 2004;164:1275-84.

64 Carnahan J, Wang P, Kendall R, et al. Epratuzumab, a humanized monoclonal antibody targeting CD22: characterization of in vitro properties. Clin Cancer Res 2003;9:3982S-90S.

65 Isaksen K, Jonsson R, Omdal R. Anti-CD20 treatment in primary Sjögren's syndrome. Scand J Immunol 2008;68:554-64.

66 Gottenberg JE, Cinquetti G, Larroche C, et al. Efficacy of rituximab in systemic manifestations of primary Sjögren's syndrome: results in 78 patients of the AutoImmune and rituximab registry. Ann Rheum Dis 2013;72:1026-31.

67 Salliot C, Finckh A, Katchamart W, et al. Indirect comparisons of the efficacy of biological antirheumatic agents in rheumatoid arthritis in patients with an inadequate response to conventional disease-modifying antirheumatic drugs or to an anti-tumour necrosis factor agent: a meta-analysis. Ann Rheum Dis 2011;70:266-71.

68 Kremer JM, Russell AS, Emery P, et al. Long-term safety, efficacy and inhibition of radiographic progression with abatacept treatment in patients with rheumatoid arthritis and an inadequate response to methotrexate: 3-year results from the AIM trial. Ann Rheum Dis 2011;70:1826-30.

69 Genovese MC, Schiff M, Luggen M, et al. Long-term safety and efficacy of abatacept through 5 years of treatment in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor inhibitor therapy. J Rheumatol 2012;39:1546-54.

70 Curtis JR, Xie F, Chen L, et al. The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents. Ann Rheum Dis 2011;70:1401-6.

71 Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. Ann Rheum Dis 2013;72 Suppl 2:ii2-34.

72 Pollard RP, Abdulahad WH, Vissink A, et al. Serum levels of BAFF, but not APRIL, are increased after rituximab treatment in patients with primary Sjögren's syndrome: data from a placebo-controlled clinical trial. Ann Rheum Dis 2013 ;72:146-8.

73 Pers JO, Devauchelle V, Daridon C, et al. BAFF-modulated repopulation of B lymphocytes in the blood and salivary glands of rituximab-treated patients with Sjögren's syndrome. Arthritis Rheum 2007;56:1464-77.

74 Kroese FGM, Abdulahad WH, Haacke E, et al. B-cell hyperactivity in primary Sjögren's syndrome. Exp Rev Clin Immunol 2014 [In press].

Chapter 8

Samenvatting

NEDERLANDSE SAMENVATTING

Het syndroom van Sjögren (SS) is een systemische auto-immuunziekte, welke wordt gekenmerkt door een chronische ontsteking van de exocriene klieren. Vooral de speeksel- en traanklieren worden aangetast, met klachten van een droge mond en droge ogen als gevolg. Naast deze organen kunnen ook vele andere weefsels en organen betrokken zijn bij SS (extraglandulaire manifestaties), zoals de gewrichten (artritis), longen, nieren (interstitiële nefritis en glomerulonefritis) en bloedvaten (vasculitis). Bovendien hebben bijna alle patiënten last van ernstige vermoeidheid. Hoe SS ontstaat, is nog niet bekend. Wel weten we dat de cellen van het immuunsysteem betrokken zijn bij het ontstekingsproces.

SS kan zowel primair (pSS) of secundair (sSS) voorkomen. Wanneer naast de betrokkenheid van exocriene klieren er ook sprake is van een andere auto-immuunziekte, zoals reumatoïde artritis (RA) of systemische lupus erythematosus (SLE), spreken we van sSS. In iets meer dan de helft van de gevallen is er sprake van sSS. De ziekte komt vaker bij vrouwen dan bij mannen voor, in de verhouding 9:1 en openbaart zich in het algemeen tussen het 20ste en 40ste levensjaar. De geschatte prevalentie van SS is 0,3-1,0%, wat SS tot de meest voorkomende systemische auto-immuunziekte na RA maakt. Desondanks wordt aanzienlijk minder onderzoek gedaan naar de behandeling van SS dan naar de behandeling van bijvoorbeeld RA en SLE.[1] Terwijl voor RA een breed scala aan traditionele 'Disease-Modifying Antirheumatic Drugs' (DMARDs) en biologische DMARDs beschikbaar is, zijn de (systemische) therapeutische opties voor SS nog beperkt.

Biologische DMARDs zijn geneesmiddelen die zeer specifiek aangrijpen op componenten van de immuunrespons, vooral op het niveau van cytokinen. De beschikbare en vermoedelijk effectieve biologische DMARDs zijn nog in onderzoek en/of nog niet geregistreerd voor toepassing in patiënten met SS.

Cytokinen zijn signaalmoleculen die voornamelijk worden geproduceerd door cellen van het immuunsysteem. Cytokinen hebben een sterk regulerend effect op zowel cellen van het immuunsysteem als op andere lichaamscellen. De uitgescheiden cytokinen induceren een cascade van reacties en hebben tal van effecten, met uiteindelijk een ontsteking als gevolg. Cytokinen kunnen in hun werking worden geremd door oplosbare cytokinereceptoren toe te dienen. Deze oplosbare cytokinereceptoren competeren met celgebonden cytokinereceptoren. Ook kunnen cytokinen worden geremd met specifieke antilichamen, de zogeheten monoklonale antilichamen. In beide gevallen bestaan de geneesmiddelen uit natuurlijke of synthetisch bereide eiwitten die een biologische interactie aangaan met de cytokinen, vandaar de term 'biologische' DMARDs.[2] Biologische DMARDs die de werking van pro-inflammatoire cytokinen tegen gaan, blijken effectieve middelen bij de behandeling van auto-immuunziekten zoals RA en SLE. Vermoedelijk zijn deze biologische DMARDS ook effectief in de behandeling SS. Voorbeelden van biologische DMARDs zijn rituximab (zie **hoofdstuk 4**) en abatacept (zie

hoofdstuk 6), het effect van deze DMARDS op de ziekteactiviteit van SS is in de studies die in deze hoofdstukken zijn beschreven onderzocht.

In dit promotieonderzoek werden een aantal onderwerpen met betrekking tot SS, en pSS in het bijzonder, nader onderzocht, namelijk (1) het effect van het hebben van SS op het dagelijks functioneren van patiënten, om de noodzaak van onderzoek naar nieuwe therapeutische opties in SS te onderschrijven en (2) de evaluatie van het effect van 2, in de inleidende paragrafen genoemde, veelbelovende biologische DMARDs (rituximab en abatacept) op het klachtenpatroon van patiënten met pSS. Met betrekking tot de behandelstudies werd gekozen voor het bestuderen van het effect van biologische DMARDs in pSS patiënten, omdat in pSS patiënten het effect van een biologische DMARD op SS beter te bestuderen is dan in sSS patiënten bij wie immers ook een andere autoimmuunziekte aanwezig is. Voor het evalueren van het effect van een therapie en het kunnen vergelijken van de effecten van verschillende therapieën is het voorts noodzakelijk om de beschikking te hebben over goed gedefinieerde en gebruiksvriendelijke meetinstrumenten. Met dergelijke meetinstrumenten kan de omvang en de ernst van pSS, en het effect van een therapie hierop, op een gestandaardiseerde manier worden vastgelegd. Daarom werd in het kader van dit promotieonderzoek tevens de EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)[3] en de EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)[4] onderzocht op hun potentie om het effect van een interventie therapie te evalueren (3).

In **hoofdstuk 2** wordt een studie gepresenteerd waarin de gezondheidsgerelateerde kwaliteit van leven, arbeidsparticipatie en arbeidsongeschiktheid in pSS en sSS patiënten wordt vergeleken met die van een steekproef afkomstig uit de Nederlandse bevolking. Aan het gehele cohort van SS patiënten, dat routinematig voor controle in het Universitair Medisch Centrum Groningen werd gezien, werd een vragenlijst gestuurd. 195 van de 235 patiënten (83%) bleken bereid te zijn om aan dit onderzoek deel te nemen en stuurden de vragenlijst terug. Analyse van de resultaten toonde aan dat SS patiënten een lagere gezondheidsgerelateerde kwaliteit van leven en een lagere arbeidsparticipatie hadden en vaker arbeidsongeschikt waren dan individuen uit een vergelijkbare gezonde populatie. Patiënten met sSS scoorden lager dat patiënten met pSS op de gebieden fysiek functioneren, lichamelijke pijn en algemene gezondheid dan pSS patiënten. De resultaten van dit onderzoek benadrukken de noodzaak tot de ontwikkeling van nieuwe therapeutische opties voor SS.

In **hoofdstuk 3** wordt de huidige behandeling van glandulaire- en extraglandulaire manifestaties van SS beschreven. Ook worden in dit hoofdstuk de toekomstperspectieven hoe SS effectief te behandelen geschetst. Hoewel er nog geen curatieve of causale behandeling bestaat voor SS, zijn er inmiddels diverse ondersteunende en symptoma-

tische therapeutische opties beschikbaar. Bovendien zijn diverse biologische DMARDs in ontwikkeling en/of worden deze middelen getest in fase I of fase II studies. Behandeling met biologische DMARDs lijkt veelbelovend, maar niet alle tot dusver onderzochte biologische DMARDs bleken effectief te zijn voor de behandeling van pSS (interventiestudies met biologische DMARDs zijn tot op heden niet verricht in patiënten met sSS). Bij RA is remming van de pro-inflammatoire cytokines tumor necrosis factor α (TNFα) en interferon α (IFN-α) klinisch succesvol gebleken. In gerandomiseerde gecontroleerde studies in pSS bleek behandeling met anti-TNFα en IFN-α echter niet effectief. Andere cytokines, zoals IL-6 en BAFF (B-cel activerende factor), adhesiemoleculen en chemokines (zoals CXCL10 en CXCL13), zijn ook mogelijke doelwitten zijn voor behandeling met biologische DMARDs. Biologische DMARDs die aangrijpen op deze doelwitten waren ten tijde van het schrijven van dit hoofdstuk nog niet onderzocht in pSS; inmiddels is een studie verschenen waarin een positief effect is gerapporteerd van de behandeling van SS met belumimab, een biologische DMARD gericht tegen BAFF.[5] Behandeling met de monoklonale antilichamen rituximab en epratuzumab, biologische DMARDs die aan grijpen op de B-cel, met o.a. B-cel depletie als gevolg, lijkt veelbelovend te zijn. Ook modulatie van het co-stimulatoire signaal tussen antigeenpresenterende cellen en T-cellen en tussen B- en T-cellen (met abatacept), een belangrijke stap in auto-immuun processen, lijkt een veel belovende therapie in pSS. In de nabije toekomst wordt een grote rol voor biologische DMARDs in de behandeling van pSS verwacht. Grotere fase II en III studies zijn nodig om de eerste veelbelovende resultaten van open-label studies en kleine gerandomiseerde gecontroleerde klinische studies met onder andere rituximab (zie **hoofdstuk 4**) en abatacept (zie **hoofdstuk 6**) te bevestigen. Inmiddels wordt het effect van rituximab in fase III studies onderzocht.

In **hoofdstuk 4.1** wordt een studie beschreven waarin de effectiviteit en veiligheid van B-cel depletie met rituximab werd onderzocht in een dubbelblinde, placebo-gecontroleerde studie in 30 pSS patiënten. Rituximab is een chimerisch humaan-muis monoklonaal antilichaam gericht tegen het B-cel oppervlakte molecuul CD20. Rituximab bestaat uit een geglycosyleerd immunoglobuline met constante humane IgG1 regio's (Fc-deel) en variabele muizen-lichte-keten en -zware-keten regio's (Fab-deel).[6] CD20 komt tot expressie op het celoppervlak van pre-B, transitionele B en mature B lymfocyten en gaat verloren in het plasmacel stadium. CD20 medieert B-cel activatie, proliferatie en differentiatie.[7,8] CD20 speelt een belangrijke rol in de ontwikkeling van T-cel onafhankelijke antilichaamresponses.[9] Het Fab-deel van rituximab bindt aan het CD20 antigeen op B-lymfocyten. Het Fc-deel kan immunologische effectorfuncties activeren wat resulteert in dood van B-cellen. Mogelijke mechanismen van de effector-gemedieerde celdood zijn antilichaam afhankelijke cellulaire cytotoxiciteit (apoptose) en complement-afhankelijke cytotoxiciteit (cellysis). Ook is aangetoond dat binding van rituximab aan het CD20 antigeen op B-cellen rechtstreeks celdood via apoptose induceert.[6]

Van de 30 geïncludeerde patiënten met vroege pSS werden 20 patiënten behandeld met rituximab en 10 patiënten met placebo. Alle patiënten kregen een korte kuur met corticosteroïden (5 dagen) om het ontwikkelen van bijwerkingen, in het bijzonder een op serumziekte gelijkend klachtenpatroon, te voorkomen. Behandeling met rituximab resulteerde in een verbetering van zowel objectieve als subjectieve parameters van de aan pSS gerelateerde ziekteactiviteit. De speekselklierfunctie verbeterde, de vermoeidheid verminderde en het aantal extraglandulaire manifestaties (betrokkenheid van organen die buiten de exocriene klieren zijn gelegen) nam af. De meeste verbeteringen werden 12 tot 36 weken na behandeling met rituximab waargenomen.
Op basis van de veelbelovende resultaten van dit placebo-gecontroleerde onderzoek met rituximab, werd een extensie onderzoek uitgevoerd naar de werkzaamheid van herbehandeling met rituximab (**hoofdstuk 4.2**). In deze studie werden de data geanalyseerd van 15 pSS patiënten die hun eerste cyclus met rituximab kregen tijdens de placebo-gecontroleerde studie (**hoofdstuk 4.1**) en de tweede cyclus met rituximab tijdens de daarop volgende extensiestudie. Herbehandeling met rituximab resulteerde in vergelijkbare gunstige effecten als initiële behandeling in objectieve parameters, waaronder de ziekteactiviteit gemeten met ESSDAI,[3] terwijl het effect op de patiënt-gerapporteerde parameters iets minder uitgesproken was dan tijdens de eerste cyclus. Het beoogde doel van herbehandeling met rituximab is het bewerkstelligen van langdurige effectiviteit van deze behandeling en daarmee het voorkomen van opvlammingen van de ziekte. Daarom zijn verdere studies nodig naar de optimale timing (dus voor terugkeer van symptomen) van herbehandeling met rituximab in patiënten met pSS.
In **hoofdstuk 4.3** worden de uitkomsten van de tussen januari 2000 en januari 2011 gepubliceerde open-label en gerandomiseerde gecontroleerde studies in pSS patiënten met rituximab geanalyseerd en kritisch beschouwd. Zowel in open-label studies als in gerandomiseerde gecontroleerde studies werd aangetoond dat behandeling met rituximab onder andere resulteert in een afname van extraglandulaire manifestaties en vermoeidheid en in een toename van gezondheidsgerelateerde kwaliteit van leven. Een positief effect op het niveau van de speekselsecretie bleek afhankelijk te zijn van de secretoire potentie van de speekselklieren voorafgaande aan de behandeling met rituximab (het basisniveau van de speekselproductie is gerelateerd aan ziekteduur; hoe korter de duur van de ziekte, hoe hoger de resterende speekselproductie). Patiënten met een korte ziekteduur toonden meer verbetering dan patiënten met langere ziekteduur, onder meer ten aanzien van sicca klachten, vermoeidheid en gezondheidsgerelateerde kwaliteit van leven. Het positieve effect van rituximab op de speekselklieren, zowel qua functie als op klierweefsel niveau, onderstreept de effectiviteit van B-cel depletie therapie met rituximab. De belangrijkste conclusie uit dit overzicht is dat behandeling met rituximab weliswaar veelbelovend is, maar dat aanvullend onderzoek nodig is om te bepalen welke pSS patiënten het meest zullen profiteren van deze therapie.

Om de effectiviteit van biologische DMARDs zoals rituximab (**hoofdstuk 4**) en abatacept (**hoofdstuk 6**) te onderzoeken, zijn, zoals in de inleiding bij deze samenvatting al is gesteld, goed gedefinieerde en gebruiksvriendelijke instrumenten om de omvang en de ernst van pSS (ziekteactiviteit) op een gestandaardiseerde manier te onderzoeken van groot belang. Onlangs zijn twee meetinstrumenten ontwikkeld, de ESSDAI en de ESSPRI, die deze rol zouden kunnen vervullen in pSS.[3] De ESSPRI is een vragenlijst die wordt ingevuld door de patiënt. Hiermee kunnen de symptomen (pijn, droogheid en vermoeidheid) die de patiënt ervaart worden gemeten. De ESSDAI is een index welke wordt ingevuld door de behandelende arts. Hiermee worden de systemische verschijnselen (bijvoorbeeld gewrichtsklachten, nierfunctiestoornissen of bloedafwijkingen) geobjectiveerd. Prospectieve gegevens over de responsiviteit (het kunnen meten van verandering) van de ESSDAI en de ESSPRI na therapeutische interventie in pSS patiënten ontbreken echter. Responsiviteit is de mate waarin een meetinstrument veranderingen in een variabele in de tijd kan vaststellen. Het doel van het in **hoofdstuk 5.1** beschreven onderzoek was het evalueren van de responsiviteit van de ESSPRI en de ESSDAI in 28 patiënten met pSS die werden behandeld met rituximab. Deze studie toonde aan dat de ESSDAI en de ESSPRI gevoelige meetinstrumenten zijn voor het meten van veranderingen in ziekteactiviteit na therapeutische interventie. Deze bevindingen onderschrijven de bruikbaarheid van beide indices voor toekomstige klinische studies in patiënten met pSS. De responsiviteit van de ESSDAI was groter dan van de ESSPRI.
Om de bruikbaarheid van de ESSDAI in klinische studies verder te onderzoeken, werd in **hoofdstuk 5.2** de responsiviteit van de ESSDAI in de binnen onze onderzoeksgroep verrichte dubbelblinde, placebo-gecontroleerde, gerandomiseerde studie met rituximab onderzocht. In deze gerandomiseerde studie waren de gegevens nodig om de verschillende ESSDAI domeinen te scoren, prospectief verzameld. De responsiviteit van de ESSDAI was sterk verschillend tussen de rituximab groep en de placebo groep. Dit resultaat onderschrijft dat de ESSDAI een gevoelig meetinstrument is voor het meten van verandering in ziekteactiviteit in de tijd. De ESSDAI op week 24 is een goed eindpunt voor het beoordelen van de effectiviteit van rituximab.

In **hoofdstuk 6** worden de resultaten van de open label Actieve Sjögren Abatacept Pilot (ASAP) studie gepresenteerd. Abatacept is een volledig humaan fusiemolecuul van IgG-Fc en cytotoxische T-lymfocyt antigeen 4. Abatacept moduleert de CD28-gemedieerde T-cel co-stimulatie. Co-stimulatie tussen antigeen presenterende cellen en T-cellen, en tussen B-cellen en T-cellen is een essentiële stap in T-cel afhankelijke immuunresponsen. Auto-immuunreacties, zoals aanwezig bij SS, behoren tot deze immuunresponsen.[10] In deze studie werden 15 patiënten met vroege en actieve pSS behandeld met abatacept om de werkzaamheid en veiligheid hiervan te onderzoeken. De ziekteactiviteit (gemeten met ESSDAI en ESSPRI) en de reumafactor en IgG spiegels in het serum daalden tijdens behandeling met abatacept en stegen weer in de periode na beëindiging van de behan-

deling. Er werd geen verbetering gezien van de speeksel- en traanklierfunctie tijdens de behandeling met abatacept. Behandeling met abatacept bleek wel te leiden tot een significante afname van de vermoeidheid en tot een significante toename van de gezondheidsgerelateerde kwaliteit van leven. Ernstige bijwerkingen of infecties deden zich niet voor. Uit deze open-label studie komt naar voren dat behandeling met abatacept effectief en veilig is en dat abatacept goed wordt verdragen.

Referenties

1 Fox RI. Sjögren's syndrome. Lancet 2005;366:321-31.

2 Immunologie. Rijkers GT, Kroese FGM, Kallenberg CGM, Derksen RHWM. Bohn Stafleu van Loghum, Houten, 2009.

3 Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: Development of a consensus systemic disease activity index for primary Sjögren's syndrome. Ann Rheum Dis 2010;69:1103-9.

4 Seror R, Ravaud P, Mariette X, et al. EULAR Sjögren's syndrome patient reported index (ESSPRI): Development of a consensus patient index for primary Sjögren's syndrome. Ann Rheum Dis 2011;70:968-72.

5 Mariette X, Seror R, Quartuccio, et al. Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis. 2013 [Epub ahead of print].

6 Mabthera. Samenvatting van de productkenmerken. Versie november 2013.

7 Tedder TF, Boyd AW, Freedman AS, et al. The B cell surface molecule B1 is functionally linked with B cell activation and differentiation. J Immunol 1985;135:973-9.

8 Tedder TF, Forsgren A, Boyd AW, et al. Antibodies reactive with the B1 molecule inhibit cell cycle progression but not activation of human B lymphocytes. Eur J Immunol 1986;16:881-7.

9 Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest 2010;120:214-22.

10 Reiser H, Stadecker MJ. Costimulatory B7 molecules in the pathogenesis of infectious and autoimmune diseases. N Engl J Med 1996;335:1369-77.

List of abbreviations

List of abbreviations

AAV	anti-neutrophilic cytoplasmic antibodies associated vasculitis
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
AE(s)	adverse events
AECG	American-European Consensus Group
ANA	antinuclear antibody
APRIL	a proliferation-inducing ligand
ASAP	Active Sjögren Abatacept Pilot
BAFF	B-cell activating factor
BlyS	B-lymphocyte stimulator
CBC	complete blood cell count
CHOP-R	cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab
CNS	central nervous system
Cr	creatinine
CRP	C-reactive protein
CTLA-4	cytotoxic T-lymphocyte antigen 4
DAS28	disease activity score 28
DC	disability compensation
DHEA	Dehydroepiandrosterone sulphate
ds-DNA	double-stranded DNA
DMARD(s)	Disease-Modifying Antirheumatic Drug(s)
EBV	Epstein-Barr virus
EGM	extraglandular manifestation
ENA	extractable nuclear antigens
ESR	erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR	European League Against Rheumatism
ES	effect size
GDA	global disease activity
GEE	generalised estimating equations
HIV	human immunodeficiency virus
HR-QoL	health-related quality of life
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IVIG	intravenous immunoglobulins
MALT	mucosa-associated lymphoid tissue
MFI	Multidimensional Fatigue Index
MMF	Mycophenolate Mofetil
NHL	non-Hodgkin's lymphoma
NSAIDs	nonsteroidal anti-inflammatory drugs
PNS	peripheral nervous system
pSS	primary Sjögren's syndrome
RA	rheumatoid arthritis
RCT	randomised controlled trial
RF	rheumatoid factor

SAE(s)	serious adverse event(s)
SF-36	Short Form 36 questionnaire
SLE	systemic lupus erythematosus
SPEP	serum protein electrophoresis
SRM	standardised response mean
SS	Sjögren's syndrome
sSS	secondary Sjögren's syndrome
SWS	stimulated whole salivary flow rate
TBUT	tear break-up time
TNFα	tumor necrosis factor α
TSH	thyroid stimulating hormone
TRIPPS	Trial of Remicade In Primary Sjögren's Syndrome
U/A	urinalysis
UMCG	University Medical Center Groningen
UWS	unstimulated whole salivary flow rate
VAS	visual analogue scale

Dankwoord

Science, like all creative activity, is exploration, gambling, and adventure. It does not lend itself very well to neat blueprints, detailed road maps, and central planning. Perhaps that's why it's fun.

-HA Simon, 1964-

Zonder de hulp van vele anderen had ik deze reis vol avontuur niet kunnen maken en zeker niet tot een succesvol einde kunnen brengen. Een aantal mensen wil ik hiervoor graag persoonlijk bedanken.

Allereerst wil ik de patiënten bedanken die hebben deelgenomen aan de diverse onderzoeken zoals beschreven in dit proefschrift.

Prof dr LGM de Bont wil ik bedanken voor de mogelijkheid die ik heb gekregen om dit onderzoek te combineren met de studie tandheelkunde en voor mijn opleidingsplaats binnen de afdeling MKA chirurgie.

Mijn promotoren wil ik bedanken voor al hun begeleiding. Prof dr A Vissink, beste Arjan, ik had mij geen betere 1e promotor kunnen wensen! Natuurlijk ben je snel en goed in je werk als onderzoeksbegeleider, maar het zijn juist ook andere persoonlijke kwaliteiten waarover jij beschikt, die ik erg in je waardeer. In de afgelopen jaren ben je een enthousiaste, stimulerende en begripvolle leermeester gebleken. Je wist mij aan te moedigen op het juiste moment en mij subtiel aan te sporen wanneer dat nodig was. Je deed dit altijd op een positieve, opbouwende manier. Dit heeft gemaakt dat ik me zowel op wetenschappelijk als op persoonlijk vlak door je gesteund hebt gevoeld. Dank voor je vertrouwen in mij.
Prof dr H Bootsma, beste Hendrika, we hebben in de afgelopen jaren veel meegemaakt en gedeeld. Ik kijk hier met een warm en positief gevoel op terug. Samen brachten we tijd door met het brainstormen over de opzet van nieuwe studies, de interpretatie van resultaten en over welke aspecten belangrijk zouden kunnen zijn voor de discussie. Maar dit alles gebeurde nooit zonder dat je vroeg hoe het met me ging. Ik kon altijd bij je binnenlopen. Samen bezochten we onder andere congressen in Parijs, Brest (wat een wereldstad), San Francisco en Kyoto (prachtig!). Dit zijn slechts enkele voorbeelden van de vele mooie en waardevolle momenten die we hebben gedeeld. Ik heb veel van je mogen leren, dank voor je persoonlijke aanpak hierbij.
Prof dr FKL Spijkervet, beste Fred, net als Hendrika ben jij tijdens mijn onderzoekstraject opleider, afdelingshoofd en hoogleraar geworden en daarmee van co-promotor promotor. Alle parotisbiopten van de klinische studies zijn door jou genomen. Deze biopten vormen een belangrijke peiler van het onderzoek dat binnen ons Sjögrenteam wordt verricht. Tijdens de polimiddagen op donderdag kon ik altijd een beroep op je doen voor overleg. Naast je klinische betrokkenheid, bewaakte je niet alleen de goede logis-

tiek rondom de klinische studies, maar ook de planning van mijn promotieonderzoek in relatie tot mijn studie tandheelkunde en mijn recent gestarte opleiding tot MKA chirurg. Bedankt voor je begeleiding.
Prof dr FGM Kroese, beste Frans. Bij binnenkomst in het Sjögrenteam werd je kracht meteen duidelijk: je zit boordenvol enthousiasme, nieuwe ideeën en energie. Je hecht bovendien veel belang aan de koppeling tussen biologie en kliniek. Een wetenschapper moet in staat zijn om in lekentaal uit te kunnen leggen waar hij zich mee bezig houdt, is een van jouw motto's. Jij hebt mij onvermoeibaar wegwijs proberen te maken in de wondere wereld van de immunologie. Ook beklommen we samen met Annie en Sylvia Mount Fuij, dit was zowel letterlijk als figuurlijk een hoogtepunt! Bedankt voor je prettige begeleiding.

De leden van de beoordelingscommissie, Prof dr TWJ Huizinga, Prof dr JM van Laar en Prof dr FR Rozema, ben ik zeer erkentelijk voor het beoordelen van mijn manuscript.

Mijn paranimfen. Dr M Jalving, lieve Hilde, toen jij in 2006 promoveerde en ik de kaft van jouw proefschrift ontwierp, spraken we af dat, als ik ooit zou gaan promoveren, jij de inhoud van mijn proefschrift zou schrijven en ik weer de omslag zou maken. Dit was immers een gebleken succesvolle formule. Hoe anders is het gelopen! Ook de taak van het ontwerpen van de kaft is inmiddels vergeven, maar ik ben heel erg blij, dankbaar en trots dat jij, net als altijd, ook tijdens mijn promotie naast mij wilt staan! Je bent een vriendin voor het leven en ik hoop dat we samen nog heel veel mooie momenten zullen beleven.
Drs EWJ de Boer, lieve Esther. Kort na elkaar begonnen we als onderzoekers op de afdeling MKA chirurgie. Het klikte goed en naast collega's werden we ook vriendinnen. We hebben veel gesproken over het (onderzoeks-)werk, maar vooral ook over alle andere belangrijke zaken in het leven. Ik waardeer je ruime blik en je eerlijkheid enorm. Ook in de afrondende fase van mijn proefschrift bleek je van onschatbare ware! Bedankt voor je vriendschap. Prachtig dat je mijn paranimf bent.

Mijn mede-Sjögrenonderzoekers. Dr JM Meijer, lieve Jiska, via jou ben ik in het Sjögrenonderzoek beland. Dit heeft niet alleen geresulteerd in een aantal mooie, gemeenschappelijke publicaties, maar ook in veel plezier. Inmiddels heb jij een ander prachtig pad gekozen; ik heb bewondering voor de keuzes die je hebt gemaakt. Ik vind het erg fijn dat we elkaar nog regelmatig zien om bij te praten!
Dr RPE Pollard, beste Rodney, samen zijn wij begonnen aan dit traject waarin we ons onderzoek combineerden met onze studie tandheelkunde. We hadden niet alleen ons onderzoeksonderwerp gemeen, ook hebben we samen eindeloos 'geDOT' en waren we kliniekpartners. Bedankt voor je steun en gezelligheid in de afgelopen jaren. Ik verheug me op onze samenwerking als AIOS MKA chirurgie.
Dr S Arends, beste Suzanne, bedankt voor al je hulp, zonder jou was dit proefschrift nog

niet afgerond. Je bent altijd bereid geweest om me nieuwe analyses te leren, met me mee te denken en mee te schrijven. Ik hoop dat we dat nog vaker samen zullen doen. Ook op de tennisbaan speelde ik nog nooit zo goed als naast jou; erg leuk om eens in de damesdubbel 3 mee te kunnen doen en zelfs een wedstrijd te winnen!
Leden van het Groningse Sjögrenteam, beste allemaal, bedankt voor alle boeiende discussies tijdens onze wekelijkse bijeenkomsten en de plezierige samenwerking.
Drs K Delli, drs EA Haacke, drs TA van der Meulen, drs RV Moerman, drs JF van Nimwegen en drs GMPJ Verstappen, beste Konstantina, Erlin, Taco, Rada, Jolien en Gwenny, bedankt voor de prettige samenwerking en veel succes met het vervolgonderzoek in ons Sjögrenteam.

J Bulthuis-Kuiper, beste Janita, jij was onmisbaar bij alle logistiek rondom de klinische studies met rituximab en abatacept. Alles was goed voor elkaar. Je dacht mee over de onderzoeksprotocollen, hoe we de data konden verzamelen, plande vele afspraken en bezocht alle patiënten op het centrum voor dagbehandeling. Het invoeren van de vragenlijsten en de labwaarden is een grote klus geweest. Heel erg bedankt voor je al hulp!
GS van Zuiden, beste Greetje, in jouw rol als verpleegkundig specialist in opleiding droeg jij onder andere zorg voor onze studiepatiënten op het centrum voor dagbehandeling. Dank voor je inzet!

Ik wil alle medewerkers op de polikliniek MKA chirurgie, in het bijzonder Jenny van den Akker en Miranda Been, bedanken voor de hulp bij de vele patiëntenonderzoeken.
Judith Baldi, Wendy van der Goot-Roggen, Hester Groenewegen, Steven Loomans, Sitske Oort, Monique Stokman en Carla Zegger, bedankt voor jullie hulp bij de speekselafnames.
Anne Wietsema en Ashwin Beekes, speekselbuisjes wegen wordt een stuk leuker wanneer je in goed gezelschap verkeerd. Dank daarvoor.
Alle medeonderzoekers en oud-kamergenootjes op de 3e verdieping en de AIOS MKA chirurgie wil ik bedanken voor de plezierige samenwerking en de gezellige afleiding.
Dr J Huddleston-Slater, beste James, mijn eerste artikel schreef ik onder andere samen met jou. Samen nadenken over methodologie, op pad om de data van het CBS te analyseren en de resultaten interpreteren; ik vond het een erg leuk begin van mijn onderzoekercarrière op onze afdeling, bedankt voor je hulp!
Dr SAHJ de Visscher, beste Sebastiaan, we zitten niet alleen in dezelfde kamer op de 3e, maar ook in hetzelfde schuitje. We delen het enthousiasme over het doen van onderzoek, maar ook de daarbij horende frustraties. Het was prettig dat ik steeds met je heb kunnen sparren. Ook vind ik het erg leuk dat ik via jou Selma heb leren kennen!
Lisa Kempers, Nienke Jaeger, Fieke Wiersema, Angelika de Vries en Harrie de Jonge wil bedanken voor de gezelligheid, af en toe een luisterend oor en natuurlijk ook voor de administratieve, logistieke en technische ondersteuning.

Het dagelijks bestuur, Dr B van Minnen en R Rolvink, beste Baucke en Richard, bedankt voor jullie begrip en jullie oplossingen, om ook tijdens het begin van mijn opleiding toch ook ruimte creëren om mijn proefschrift af te ronden.

De afdeling reumatologie en klinische immunologie wil ik bedanken voor de prettige samenwerking. In het bijzonder wil ik dr Liesbeth Brouwer en Martha Leisma bedanken voor de medewerking aan het klinische deel van de studies.
Eefke Eppinga, Diana Nijborg, Ragonda Tjemmes, Janny Wever en Kiki Bugter wil ik bedanken voor alle logistieke ondersteuning.
Drs J Bijzet, Prof dr PC Limburg, dr C Roozendaal en dr J Westra. Beste Johan, Piet, Caroline en Hannie, bedankt voor de goede samenwerking.
Dr WH Abdulahad en MG Huitema, beste Wayel en Minke, bedankt voor al jullie inspanningen voor de klinische studies in het laboratorium. Wayel, je enthousiasme werkt aanstekelijk; het is leuk om met je samen te werken.
A Visser en S Beijer, beste Annie en Sylvia, bedankt voor jullie bijdrage aan dit proefschrift.

Drs N Sillevis Smitt-Kamminga, beste Nicole, veel dank ben ik jou en je collega's verschuldigd voor het verzamelen van alle oogheelkundige data voor de klinische studies, daar heeft heel veel tijd in gezeten!

Mijn vrienden bedank ik graag voor de ondersteuning en de hoognodige afleiding. Lieve, vrolijke, slimme, bedachtzame, grappige en trouwe studievriendinnetjes: Djoeke, Hilde, Jitske, Lieveke, Sieneke en Susan. We hebben samen een heerlijke studententijd gehad en wat fijn dat het altijd goed, relativerend, grappig, gezellig en verhelderend is als we elkaar weer zien.
Lieve Marit en Patrick, zware tijden zullen altijd je echte vrienden onthullen, bedankt voor jullie ware vriendschap!
Beste tennisvrienden, bedankt voor de gezelligheid op, naast en buiten de tennisbaan.
Beste Mattia, wat gezellig dat je in Groningen bent komen wonen, nu ook samen met Leonie. Bedankt voor je kritische beoordeling van teksten. Bedankt voor je vriendschap.

Lieve Karen, Erik, Ingrid, Paul, Anne-Britt, Lukas en (kleine) Matthijs. Wat ben ik gek op jullie! Bedankt voor alle fijne, gezellige en liefdevolle niet werkgerelateerde momenten in de afgelopen jaren. Lieve overige familie en vrienden, bedankt voor jullie steun en interesse.

Lieve papa en mama, een paar zinnen in dit dankwoord zullen nooit de lading kunnen dekken wat jullie voor mij betekenen. Juist in de afgelopen jaren heb ik mogen ervaren dat jullie altijd voor mij klaar staan. Bedankt voor jullie onvoorwaardelijke liefde, steun, praktische hulp, belangstelling en eindeloze geduld. Jullie hebben me geleerd om het beste uit mijzelf te halen. Ik hou van jullie!

Lieve Matthijs, wat goed dat ik die bewuste dag in september besloot ergens anders mijn boodschappen te doen. Wat is het leuk om met jou samen te zijn! Je eerlijke, oprechte en warme 'zijn', zonder opsmuk, maar met veel passie, maakt dat ik me waar we ook gaan bij jou thuis voel. Ik hou van je!

"Love can rebuild the world, they say, so everything's possible when it comes to love."
-Haruki Murakami, 2002-

CURRICULUM VITAE

Petra Mariëlle Meiners was born on August 4th 1979 in Groningen, The Netherlands. After finishing secondary school in 1998 at the 'Deltion College Zwolle', she started her medical education at the University of Groningen. After obtaining her medical degree (MD) in 2005, she worked at the department General Surgery of the Martini Hospital, Groningen and at the department of Plastic and Reconstructive Surgery of the Maxima Medical Center, Eindhoven. In 2008 she started her PhD research at the department of Oral and Maxillofacial Surgery of the University Medical Center Groningen. This work was combined with her dental training at the University of Groningen. In 2013 she started her Oral and Maxillofacial Surgery residency at the department of Oral and Maxillofacial Surgery of the University Medical Center Groningen (head Prof dr FKL Spijkervet, former head Prof dr LGM de Bont).

Address for correspondence
PM Meiners
University Medical Center Groningen
Department of Oral and Maxillofacial Surgery
9700 RB Groningen
The Netherlands

List of publications

Meiners PM, Vissink A, Kroese FG, Spijkervet FK, Sillevis Smitt-Kamminga N, Abdulahad WH, Bulthuis-Kuiper J, Brouwer E, Arends S, Bootsma H. Abatacept treatment reduces disease activity in early primary Sjogren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis 2014; doi: 10.1136/annrheumdis-2013-204653 [Epub ahead of print].

Moerman RV, Arends S, **Meiners PM**, Brouwer E, Spijkervet FK, Kroese FG, Vissink A, Bootsma H. EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) is sensitive to show efficacy of rituximab treatment in a randomised controlled trial. Ann Rheum Dis 2014;73:472-4.

Pollard RPE, Abdulahad WH, Bootsma H, **Meiners PM**, Spijkervet FKL, Huitema MG, Burgerhof JGM, Vissink A, Kroese FGM. Decrease of pro-inflammatory cytokines after B cell depletion therapy in patients with primary Sjögren's syndrome. Ann Rheum Dis 2013;72:2048-50.

Meiners PM, Arends S, Brouwer E, Spijkervet FKL, Vissink A, Bootsma. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. Ann Rheum Dis 2012;71:1297-302.

Meijer JM, Vissink A, **Meiners PM**, Bootsma H. Sjögren's syndrome: treatment and treatment evaluation. NT Reumatol 2011;3:20-24.

Meiners PM, Vissink A, Kallenberg CG, Kroese FG, Bootsma H. Treatment of primary Sjögren's syndrome with anti-CD20 therapy (rituximab). A feasible approach or just a starting point? Expert Opin Biol Ther 2011;11:1381-94.

Abdulahad WH, Meijer JM, Kroese FG, **Meiners PM**, Vissink A, Spijkervet FKL, Kallenberg CGM, Bootsma H. B-cell reconstruction and T-helper-cell balance after rituximab treatment of active primary Sjögren's syndrome. Arthritis and Rheumatism 2011;63:1116-23.

Meiners PM, Meijer JM, Vissink A, Bootsma H. Chapter 12. Management of Sjögren's syndrome. In: MH Weisman, ME Weinblatt, JS Louie, R van Vollenhove (eds). Targeted treatment of rheumatic diseases. Saunders, 2010.

Meijer JM, **Meiners PM**, H Bootsma, A Vissink. Chapter 17. Antibodytherapy in Sjögren's syndrome. Het tandheelkundig jaar 2010.

Meijer JM, **Meiners PM**, Vissink A, Spijkervet FKL, Abdulahad W, Kamminga N, Brouwer E, Kallenberg CGM, Bootsma H. Effective rituximab treatment in primary Sjögren's syndrome: a randomised, double-blind, placebo-controlled trial. Arthritis and Rheumatism 2010;62:960-968.

Meijer JM*, **Meiners PM***, Huddleston Slater JJR, Spijkervet FKL, Kallenberg CGM, Vissink A, Bootsma H. Health related quality of life, employment and disability in patients with Sjögren's syndrome. Rheumatology 2009;48:1077-1082. *Both authors contributed equally to this paper.

Meiners PM, Leon-Villapalos J, Dziewulski P. Pneumococcal septicaemia with purpura fulminans in an 11-month-old child: a case report. Journal of Plastic, Reconstructive and Aesthetic Surgery 2006; 59:1377-1380.

Meiners PM, Coert JH, Robinson PH, Meek MF. Impairment and employment issues after nerve repair in the hand and forearm. Disability and Rehabilitation 2005;27:617-623.

Gooi een steen na de dag,
zo ver als je kunt.
Spoel het zout van je huid,
doof het vuur.
Volg het spoor wat er ligt,
zoek niet wat er nooit meer is.
Was het zand uit je haar,
geef een naam aan ieder jaar.
Drink de tranen van je hand,
zwijg ervan.
Erf de ogen van je kind,
kijk er door.
Koester je geheime hart,
tot het eind.

Reis ver, drink wijn, denk na,
lach hard, duik diep,
kom terug.

Droom een boot in de zon,
geef hem zeilen en wind.
Kus een droevige mond,
heel zacht,
voor de dag begint.
Bewaar een steen in je tas,
uit het land waar je sliep,
waar je de wonden op liep,
waar het koninkrijk verging.
Haal de parels uit de zee,
geef ze weg.
Vecht met alles wat je hebt,
verlies het goed.
Wacht dan tot het lichter wordt,
je hebt de tijd.

Reis ver, drink wijn, denk na,
lach hard, duik diep,
kom terug.

Lach hard, duik diep,
kom terug.

Spinvis - Kom Terug

The printing and distribution of this thesis was financially supported by:

Nederlandse Vereniging voor Mondziekten, Kaak- en Aangezichtschirurgie	www.nvmka.nl
Nederlandse Maatschappij tot bevordering der Tandheelkunde	www.tandartsennet.nl
Rijksuniversiteit Groningen	www.rug.nl
The Graduate School of Medical Sciences	
Reumafonds	www.reumafonds.nl
Mondzorg Midden Drenthe	www.mmdbeilen.nl
De Mondenhoek	
Tandprothetische praktijk Rolink	
Verodent	
Crown Affairs – Pieter Beekwilder	www.crownaffairs.nl
Nationale Vereniging Sjögren Patiënten	www.nvsp.nl
Dentaid Benelux B.V.	www.dentaid.nl
Mundipharma Pharmaceuticals B.V.	www.mundipharma.nl
Nederlandse Vereniging van Mondhygiënisten	www.mondhygienisten.nl
Pfizer B.V.	www.pfizer.nl
Van Velthuysen Liebrecht	www.velthuysenliebrecht.nl
Gerrit van Dijk Tandtechnisch Laboratorium	
Straumann B.V.	www.straumann.nl
JDS Automatisering B.V.	www.jds-dental.nl
Roche Nederland B.V.	www.roche.nl
Dam Medical B.V.	www.dammedical.nl
ExamVision Benelux	www.examvision.nl
Noord Negentig	www.noordnegentig.nl
ABN AMRO Bank N.V.	www.abn-amro.nl
Robouw Medical B.V.	www.robouwmedical.nl
Tandtechnisch Laboratorium Laverman	www.ttllaverman.nl
Nederlandse Vereninging van Tandartsen – NVT	www.nvt.nu
J.B.B. Veldkamp, tandarts	